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Photochemical transformations in some cyclopropyl ketones

R P Gandhi*, R C Aryan & M P S Ishar
Department of Chemistry, Indian Institute of Technology- Delhi,
Hauz Khas, New Delhi 110 016

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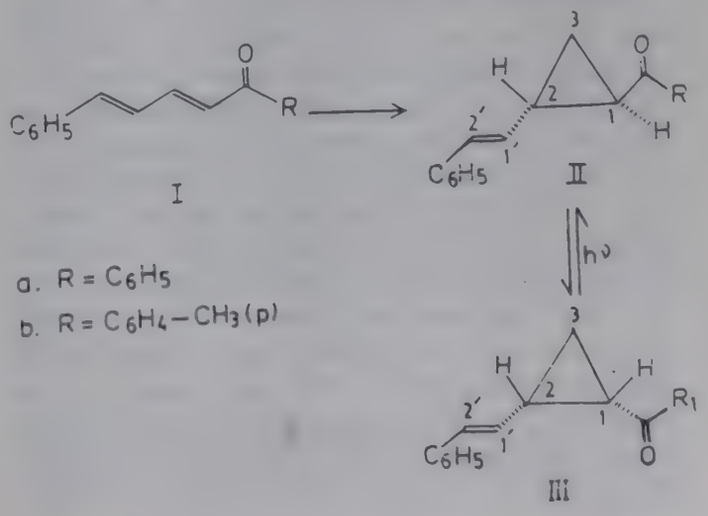
Irradiation of *trans*-1-benzoyl-2-*trans*-styrylcyclopropane (**IIa**) and *trans*-1-*p*-toluoyl-2-*trans*-styrylcyclopropane (**IIb**), leads to formation of *cis* disubstituted cyclopropanes (**IIIa**) and (**IIIb**) respectively. However, photolysis of *trans*-1-*trans*-cinnamoyl-2-phenylcyclopropane (**IV**) results in isomerization of the α,β-double bond to produce **V**. Photolysis of *trans*-1-*trans*-*p*-methoxycinnamoyl-2-*p*-methoxyphenylcyclopropane (**VI**), by contrast, produces only a cyclobutane dimer formulated as (**VII**). Irradiation of 7-phenyl-3-benzylidenespiro[2.5]octan-2-one (**IXa**) and 7-*p*-methoxyphenyl-3-*p*-methoxybenzylidenespiro[2.5]octan-2-one (**IXb**), under identical conditions, leads to isomerisation around the C = C bond. The structural assignments are based, interalia, on ^{13}C NMR and ^{1}H NMR spectral data.

Photochemistry of substituted cyclopropanes has been reported to be dependent on electronic characteristics and size of the substituent, as well as the extent of substitution[1]. In particular, in cyclopropanes bearing a carbonyl functionality in its immediate neighbourhood, the manner of photoreorganisation is controlled, interalia, by the degree of conjugation† between the ring and the C = O group[1,2]. (The conjugation of cyclopropane ring with an unsaturated functionality has been born out by theoretical and spectral investigations[3]).

In continuation of our earlier photochemical studies on 16α, 17α-methylenepregnenolone acetate[4], which was observed to undergo facile D ring enlargement, we have examined the photobehaviour of cyclopropanes possessing a C = C bond and a C = O group in different environments, as in *trans*-1-benzoyl-2-*trans*-styrylcyclopropane (**IIa**), *trans*-1-*p*-toluoyl-2-*trans*-styrylcyclopropane (**IIb**), *trans*-1-*trans*-cinnamoyl-2-phenylcyclopropane (**IV**) and *trans*-1-*trans*-*p*-methoxy-cinnamoyl-2-*p*-methoxyphenylcyclopropane (**VI**), 7-phenyl-3-benzylidenespiro[2,5]octan-2-one ([$\chi\alpha$), and 7-*p*-methoxyphenyl-3-*p*-methoxybenzylidenespiro[2.5]octan-2-one ([$\chi\beta$). Literature[1] records reports on *cis/trans* isomerization in some simple cyclopropyl ketones, albeit, the reported mechanistic rationalization[5] has been found to be rather inadequate to explain some of the present findings.

Initially, photochemical behaviour of **IIa,b** in which the cyclopropane ring is flanked by carbonyl group and double bond was examined. **IIa,b** were prepared from the corresponding cinnamalacetophenones (**Ia,b**) by Corey's method[6] and their structures were ascertained spectroscopically (vide experimental). Irradiation of **IIa** in benzene for 6 hr with a 125 watt medium pressure Hg arc in a pyrex glass reactor yielded a mixture of **IIa** (m.m.p., IR, ^{1}H NMR) and its *cis*-isomer, **IIIa** (separated by column chromatography). **IIIa** (m/z 248, M^+) showed the presence of a conjugated carbonyl group (IR band at 1665 cm^{-1}). That **IIIa** is a *cis*-isomer of **IIa** was revealed from its ^{13}C NMR spectrum which showed an upfield shift of all cyclopropane carbon resonances[cf.7] (δ 28.3, 26.1 and 15.2) as compared to those of **IIa** (δ 29.5, 27.1 and 18.4); understandably, the shielding effect, in *cis*-isomer (**IIIa**), is most pronounced for the unsubstituted cyclopropane ring carbon (**IIIa**, δ C_3, 15.2; **IIa**, δ C_3, 18.4). The above structural assignment (**IIIa**) was also supported by its PMR spectrum. In **IIIa**, the obtained J value of 16 Hz for olefinic-Hs (C_1'-H and C_2'H) is indicative of

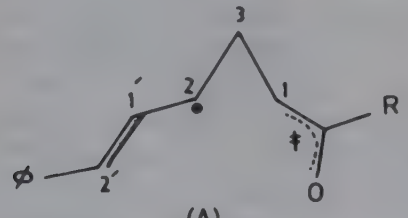


trans-geometry around the C_1'-C_2' double bond. The ratio of *cis/trans*-isomers in the steady state mixture, based on isolated yield, was 5.5 : 4.5.

Irradiation of **IIa** in methanol under similar conditions produced a mixture of **IIa** and **IIIa** in similar relative proportions.

Irradiation of **IIb** in dry benzene, under condition as described for **IIa**, produced a steady state mixture of **IIb** and **IIIb** which were separated by column chromatography over neutral alumina. The structural and stereochemical assignments in **IIIb** are based on spectral data as detailed in the case of **IIIa**. Irradiation of the cis isomer (**IIIb**) in dry benzene for 6 hr produced the same steady state mixture of **IIb** and **IIIb**.

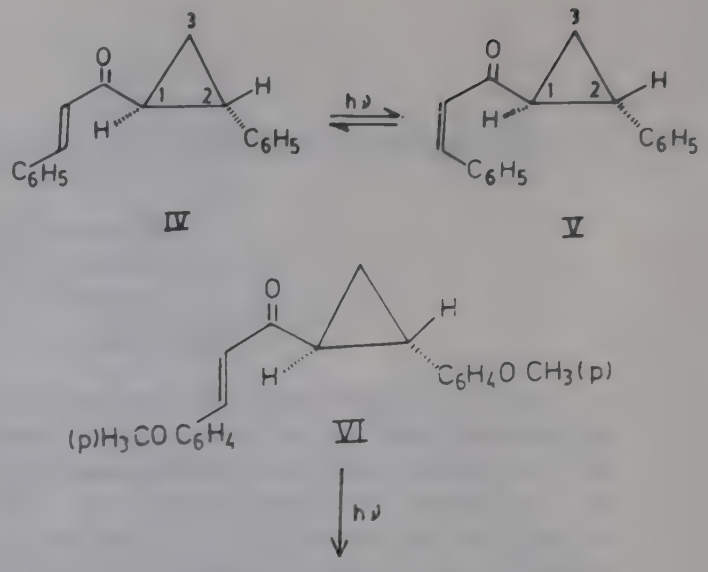
Mechanistically, the above phototransformation, **II** → **III**, involves cleavage of the most heavily substituted C_1-C_2 bond of the cyclopropane ring in **II** followed by rotation around C_2-C_3 or C_1-C_3 bond before ring closure to give the *cis*-isomer **III**. However, the intermediary species[‡] must be short lived since no isomerization around C_1'-C_2' bond has been observed. (The intermediary species is represented, after Zimmermann[6], as **A**). Alternatively, isomerization (**II** → **III**) may involve cleavage of C_1-C_3 bond of the cyclopropane ring, albeit, this is deemed less likely.



(A)

Subsequently, phototransformation of **IV** bearing aryl and cinnamoyl substituents on the cyclopropane ring was investigated. **IV** was prepared through reaction of dimethyloxosulphonium methylide with dibenzalacetone and characterized spectroscopically (vide Experimental).

Irradiation of **IV** in benzene and cyclohexane solvents for 6 hr each under conditions as employed for **IIa** gave identical mixtures of two compounds in each case (TLC), which defined all attempts at separation by repeated column chromatography. As such, the spectral data was collected on the mixture. The ^{13}C NMR spectrum of the mixture revealed cyclopropane carbon resonances, due to **IV**, at δ 31.5, 29.7 and 19.0 and, due to **V**, at δ 33.6, 30.2 and 20.0. The observation that in **V**, the cyclopropane carbons did not register any shielding in comparison to those of **IV** (rather they showed a slight deshielding of all cyclopropane carbons) suggests that no cis trans isomerization around the cyclopropane ring has occurred in the photoconversion,



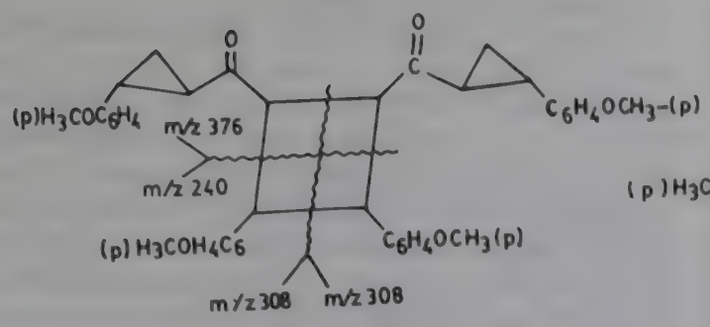
Cyclobutane dimer

IV → **V**. The assigned structures are based on ^1H NMR spectrum of the mixture (see Experimental). However, the exact ratio of *cis/trans*-isomers could not be determined in this case.

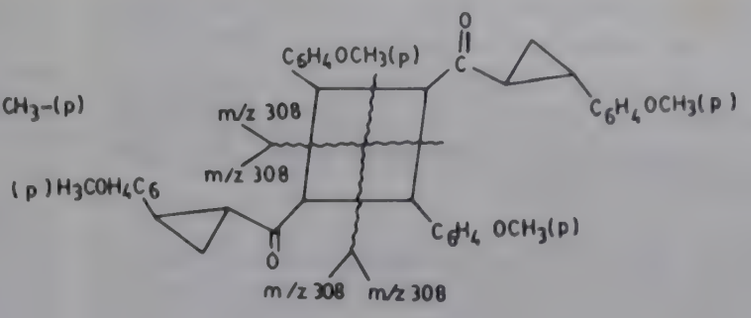
Irradiation of **VI** under similar conditions (6 hr, cyclohexane) led to a single crystalline product **VII**. From its mass spectrum (m/z 616, M^+), **VII** appeared to be a dimer of **VI**. Its IR spectrum revealed a conjugated C = O (ν_{max} at 1680 cm^{-1}), while its ^1H NMR spectrum exhibited multiplets in the region of δ 3.50-3.75, characteristic of cyclobutanes. Its ^{13}C NMR spectrum revealed a single carbonyl carbon at δ 207.6 and methine carbon resonances at δ 52.9, 51.7, 47.6 and 46.4 which indicated the presence of a cyclobutane ring in the dimer. The cyclopropane ring carbons appeared at δ 31.3, 31.0, 29.5, 28.9 and 19.1; the absence of any upfield shift of cyclopropane ring carbon resonances (with respect to δ ^{13}C values in **IV**) revealed that the *trans*-geometry around the cyclopropane rings has been retained.

Considering that (a) **VII** is a cyclobutane dimer and (b) the cyclopropanes in **VII** have *trans*-1,2-arrangement of the substituents around them, two gross structures (h-h and h-t) may be written for this compound:

A distinction between the two structures (h-h and h-t) appears possible from the mass spectrum which showed a weak peak at m/z 376 (relative abundance 5%) and an intense peak at m/z 240 (100), in addition to a peak at m/z 308 which apparently resulted from fragmentation of the h-h dimer. On the other hand, the h-t dimer is expected to give only a peak at m/z 308, irrespective of the manner of its fragmentation as shown (Chart 1). With the data available, the precise stereo-chemistry around the cyclobutane ring in the h-h dimer cannot yet be determined. However, the observation of four signals for cyclob-

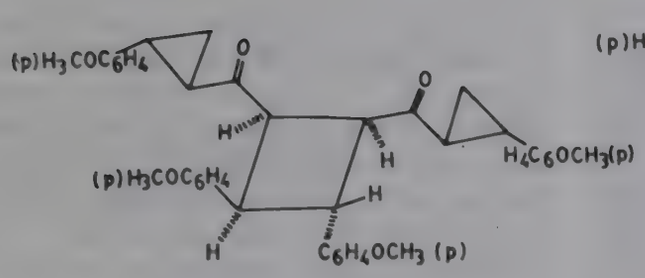


h–h

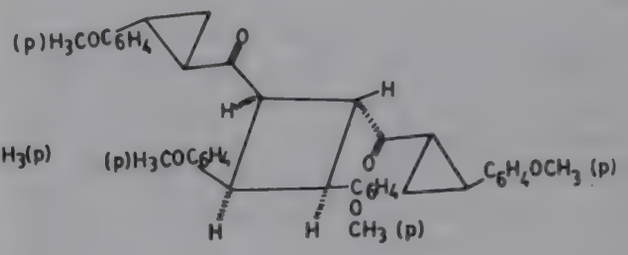


h–t

Chart 1



VII A



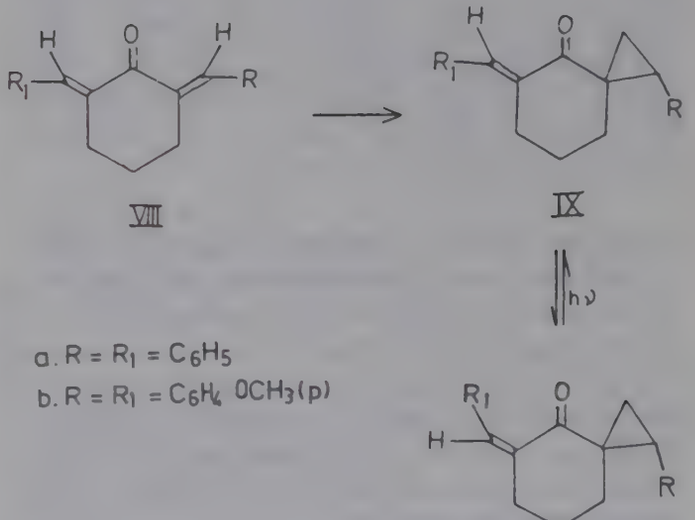
VII B

utane carbons in the ^{13}C NMR spectrum of the dimer reveals asymmetrical distribution of the substituents around all four carbons. Of the several possible structures for dimers of **VI**, two expressions which conform to the above ^{13}C NMR data are **VI-IA** and **VIIB.**

The formation of h-h dimer can be rationalized in terms of addition of a photoexcited molecule of **VI** to another molecule in the ground state[8]. The differential photobehaviour of **VI** as compared to that of **IV** (**IV** → **V**) may be related to lowering of $n \rightarrow \pi^*$ excitation energy in **VI** as a result of electron releasing $-OCH_3$ group on the aryl ring.

Irradiation of spiroketones, **IXa** and **IXb** was examined. **IXa,b** were prepared by reaction of dibenzylidene/dianisylidene cyclohexanones with dimethyloxosulphonium methylide. Their structures were determined spectroscopically (vide Experimental).

Irradiation of **IXa** in dry benzene for 6 hr, similar to that of **IIa** led to a mixture of **IXa** and **Xa** which was separated through chromatography. From its spectral data (IR, ^1H NMR and ^{13}C NMR), **Xa** was revealed to be an isomer of **IXa** with geometry around the cyclopropane ring unchanged. However, an upfield shift of C_1'-H resonance in the PMR spectrum of **Xa** (singlet at δ 6.57; in **IXa** C_1'-H is merged with aromatic-Hs resonances at δ 6.10-7.78) suggested a change in geometry around the C_3-C_1' double bond in the phototransformation, **IXa** → **Xa**. Photolysis of **IXb** under similar conditions resulted in a steady state mixture of **IXb** and **Xb. Xb** was separated through chromatography and identified spectroscopically (**Xb**, C_1'-H at δ 6.24; in **IXb** C_1'-H is merged with aromatic-Hs resonances at δ 6.80-7.64).



Experimental Procedure

IR spectra were recorded either neat (for liquids)l or KBR pellets (solids) on a Unicam SP-1200 infrared spectrophotometer, UV spectra in $CHCl_3$,

unless otherwise mentioned, on an SP-700A ultraviolet and visible spectrophotometer, NMR spectra in $CDCl_3$ on a Jeol-JNM-FX-100 FT-NMR spectrometer and mass spectra on a Jeol-JMS-D-300 spectrometer. Unless otherwise stated, pet. ether used had b.p. 60-80°.

trans-1-*Benzoyl*-2-*trans*-*styrylcyclopropane* (**IIa**)

NaH (50% suspension in oil, 0.77 g) was rendered free from oil by washing twice with dry pet. ether (40-60°) and dried in vacuum, and brought under N_2 blanket. To this was added a solution of trimethyloxosulphonium iodide (3.525 g) in dry DMSO (10 ml) and stirred for 30 min at ambient temperature. To this a solution of cinnamalacetophenone (**Ia**, 3.5 g) in DMSO (15 ml) was added, stirred overnight, and worked up by pouring into ice-cold water, whereupon a colourless solid separated out. The reaction mixture was kept in a freezer, filtered, precipitates washed thoroughly with water and crystallized from benzene-hexane (1 : 4), yield, 3.4g; m.p. 101-3°C; UV: 251 and 281 nm; IR (KBr): 1665, 1600, 1580, 1180, 1160, 1090, 1075 and 1020 cm^{-1}; ^1H NMR: δ 1.10-1.38, 1.60-1.95, 2.05-2.45 and 2.60-2.85 (multiplets, 1H each, cyclopropane ring-Hs), 5.75 (dd, 1H, J = 16 Hz and J = 8 Hz), 6.47 (bd, 1H), 7.10-8.0 (m, arom. Hs); ^{13}C NMR: δ 198.5 (C = O), 132.8, 130.4, 128.5, 127.9, 127.2, 125.7, 29.5, 27.1 and 18.4; Mass: m/z 249 (28, $M^+ + 1$), 248 (100, M^+), 230, 229, 220, 215, 157, 144, 143, 142, 141, 128, 115, 105, 91 and 77.

trans-1-*p*-*Toluoyl*-2-*trans*-*styrylcyclopropane* (**IIb**)

Cinnamal-*p*-methylacetophenone (**Ib**) was made by condensing freshly-distilled cinnamaldehyde (22 g) with p-methylacetophenone (21.5 g) in presence of NaOH (20 g) in EtOH (150 ml) and H_2O (100 ml), yellow solid, yield 30 g, m.p. 89-90° (hexane); IR (KBr): 1660, 1605, 1590, 1460 and 1360 cm^{-1}.

Ib (3.75 g) was reacted with dimethyloxosulphonium methylide generated from NaH (0.77 g) and trimethyloxosulphonium iodide (3.525 g) in DMSO (20 ml), under the conditions described for **IIa**, to give **IIb** (3.5 g); m.p. 82-83°C (hexane); UV: 259 and 285 nm; IR (KBr): 1675, 1620, 1590, 1460, 1090, 1075, 1060 cm^{-1}. ^1H NMR: δ 1.10-1.34, 1.62-1.88, 2.12-2.39, 2.60-2.84 (multiplets, 1H each, cyclopropane ring-H), 2.38 (s, 3H), 5.68-5.0 (dd, 1H; J = 16 Hz and J = 8.0 Hz), 6.38-6.65 (bd, 1H, J = 16 Hz), 7.10-7.50 (ms, arom. H); ^{13}C NMR: δ 197.9 (C = O), 143.6, 136.9, 135.3, 130.5, 129.2, 128.6, 128.2, 127.20, 125.8, 29.3, 26.9, 21.6 & 18.3; Mass: m/z 263 (38, $M^+ + 1$), 262 (100, M^+), 248, 247, 229, 171, 158, 143, 142, 141, 120, 115, 82, 79 and 65.

Irradiation of **IIa** *in benzene*

A solution of **IIa** (0.5 g) in thiophene-free dry benzene (250 ml) was irradiated in a pyrex glass reactor using a 125 watt medium pressure Hg arc for 6 hr. N_2 gas was continuously bubbled through the solution during irradiation and progress of the reaction was monitored by TLC. The solvent was removed under diminished pressure and the residual yellow oil was chromatographed over neutral alumina (25 gm, column packed in hexane). Elution with hexane (50 ml × 60) gave a colourless solid, **IIa** (0.18 g) which was crystallised from hexane, m.p. 71-72. IR: 1665, 1600, 1450, 1400, 1095, 1075, 1065 and 1030 cm^{-1}; ^1H NMR: δ 1.20-1.45, 2.10-2.50, 2.85-3.20 (multiplets, cyclopropane ring Hs), 5.90-6.30 (dd, 1H, J = 16 Hz & J = 7.5 Hz), 6.40-6.70 (d, 1H, J = 16 Hz), 7.10-7.95 (m, arom. Hs); ^{13}C NMR: δ 197.6, 137.1, 137.5, 132.6, 131.4, 128.4, 127.9, 126.9, 125.9, 28.3, 26.1, 15.2; Mass: m/z 249 (36, $M^+ + 1$), 248 (100, M^+), 175, 157, 144, 143, 142, 128, 110, 106, 105, 91, 77.

Further elution of the column gave **IIa** (0.15 g, m.p., m.m.p., IR and ^1H NMR).

Irradiation of **IIa** *in methanol*

A solution of **IIa** (0.5 g) in dry methanol (250 ml) was irradiated for 6 hr, as described above. The crude yellow oil obtained, on removal of solvent, was chromatographed over neutral alumina (25 g, packed in hexane). Elution with hexane (50 ml × 60) gave a white solid (0.18 g) which was crystallised from hexane, m.p. 71-72, undepressed on admixture with **IIIa**.

Further elution with hexane-benzene (9 : 1, 50 ml × 10) gave **IIa** (0.15 g).

Irradiation of (**IIb**) *in benzene*

A solution of **IIb** (0.5 g) in thiophene free-dry benzene (250 ml) was irradiated for 6 hr as described above. The crude yellow oil, obtained after removal of solvent, was chromatographed over neutral alumina (25 g in hexane). Elution with hexane (50 ml × 60) yielded a colourless solid, **IIIb** (0.19 g) which was crystallised from hexane. m.p. 78-79°. IR (KBr): 1675, 1620, 1590, 1460, 1090, 1075 & 1060 cm^{-1}; ^1H NMR: δ 1.28-1.56, 2.87-3.02 (ms, cyclopropane-ring-Hs), 2.4 (s, 3H), 5.98-6.30 (dd, 1H, J = 16 Hz & J = 8 Hz), 6.38-6.70 (bd, 1H, J = 16 Hz), 7.1-7.9 (m, 8H, arom. Hs); ^{13}C NMR: δ 197.1, 148.5, 135.7, 133.8, 132.8, 130.4, 129.2, 127.2, 126.8, 125.8, 27.8, 26.2, 21.6 and 15.1; Mass: m/z 263 (35, $M^+ + 1$), 262 (100, M^+), 210, 189, 171, 158, 153, 148, 142, 124, 120, 105 and 91.

Further elution of the column gave **IIb** (0.15 g,

m.p., m.m.p., ^{1}H NMR). Irradiation of **IIb** in dry methanol gave similar results.

Irradiation of cis-1-p-toluoyl-2-trans-styrylcyclopropane (**IIIb**)

A solution of **IIIb** (0.3 g) in thiophene-free benzene (250 ml) was irradiated for 6 hr under conditions as described for **IIb**. Removal of solvent under diminished pressure gave a yellow oily mixture which was separated by preparative layer chromatography (6 silica gel G coated plates, developed with hexane-benzene 1 : 1) to give **IIIb** (0.105 g, m.p., ^{1}H NMR) and **IIb** (0.08 g, m.p., m.m.p., ^{1}H NMR).

trans-1-trans-Cinnamoyl-2-phenylcyclopropane (**IV**)

This was obtained by reacting dibenzalacetone (6 g) in DMSO (50 ml) with dimethyloxosulphonium methylide generated from reaction of trimethyloxosulphonium iodide (2 g) with NaH (0.440 g) in DMSO (10 ml) as described for **IIa**. After stirring overnight, the reaction mixture was poured into ice cold water and extracted with benzene. The benzene extract was washed with water and dried (anhyd. Na_2SO_4). On removal of solvent, a yellow oil was obtained which was chromatographed over silica gel (100 g in hexane). Elution with hexane-benzene (1 : 1, 60 ml × 40) yielded **IV** as a light-yellow solid (1.6 g) m.p. 80-81° (benzene-hexane 1 : 1). UV ($CHCl_3$): 298 nm; IR: 1680, 1620, 1430, 1190, 1110, 1085 and 1060 cm^{-1}; ^{1}H NMR: δ 1.38-1.67, 1.73-1.91, 2.40-2.74 (ms, cyclopropane ring Hs), 6.89 (d, 1H, J = 16 Hz), 7.10-7.68 (m, 11H, arom./olefinic Hs); ^{13}C NMR: δ 197.8, 142.3, 130.3, 128.9, 128.8, 128.3, 126.4, 126.0, 31.6, 29.6, & 19.2; Mass: m/z 249 (25, $M^+ + 1$), 248 (100, M^+), 297, 193, 158, 157, 145, 144, 141, 131, 116, 115, 103, 91 & 77.

Irradiation of **IV** *in benzene*

A solution of **IV** (0.5 g) in thiophene-free dry benzene (250 ml) was irradiated for 6 hr as described for **IIa**. Removal of solvent under reduced pressure gave a yellow oil which was chromatographed over neutral alumina (10 g in hexane). Elution with hexane-benzene (4 : 1, 60 ml × 40) yielded a yellow oily mixture (0.4 g). IR (neat): 1680 (b), 1190, 1130, 1085 and 1060 cm^{-1}; ^{1}H NMR: δ 1.71-1.36, 1.38-1.57, 1.66-1.99, 2.05-2.23, 2.34-2.74, (ms, cyclopropane ring Hs), 6.17-6.3 (d, J = 12.7 Hz), 6.8-7.6 (m, arom./olefinic Hs); ^{13}C NMR: δ 200.3, 197.0, 141.8, 140.2, 139.8, 134.8, 130.1, 129.3, 129.0, 128.5, 128.2, 128.0, 126.8, 126.2, 126.0, 125.8, 125.6, 33.7, 31.5, 30.2, 29.3, 20.0 & 19.0.

Irradiation of **IV** in cyclohexane gave a similar mixture.

trans-1-trans-p-Methoxycinnamoyl-2-p-methoxyphenylcyclopropane (**VI**)

Dianisalacetone was made by condensing *p*-anisaldehyde (29.5 ml) with AR acetone (9.2 ml) in the presence of NaOH (25 g) in EtOH (200 ml) and H_2O (200 ml). The yellow solid was crystallized from EtOAc; yield, 28 g; m.p. 128-29, IR: 1660 cm^{-1}; ^{1}H NMR: δ 7.75-7.49 (m, 6H, arom./olefinic Hs), 6.89 (d, 4H, J = 16 Hz), 6.93 (d, 2H, J = 15 Hz), 3.81 (s, 6H, 2 × OCH_3).

VI was obtained by reacting dianisalacetone (9 g) in DMSO (15 ml) with dimethyloxosulphonium methylide [generated from NaH (0.66 g), trimethyloxosulphonium iodide (3 g) in DMSO (15 ml)] according to the procedure described for **IV**. The yellow oil obtained on removal of solvent was chromatographed over silica gel (100 g in hexane). Elution with hexane-benzene (1 : 1, 50 ml × 60) gave **VI** as a light yellow solid, crystallised from hexane-benzene (1 : 1), yield, 2.1 g, m.p. 93-94 (Found: C, 76.5; H, 6.8%. $C_{20}H_2O_3$ requires C, 77.9%, H, 6.49%); UV (MeOH) 296, 323 nm; IR: 1665, 1180, 1135, 1090, 1060, 1040 cm^{-1}; ^{1}H NMR: δ 1.31-1.49, 1.67-1.86, 2.39-2.68 (ms, cyclopropane ring Hs), 3.77 (s, 3H), 3.81 (s, 3H), 6.7-7.6 (10H, arom./olefinic Hs); ^{13}C NMR: δ 197.9, 161.5, 158.3, 141.9, 132.6, 129.9, 127.2, 134.3, 114.3, 113.9, 55.2, 31.5, 28.9 & 18.8; Mass: m/z 308 (22, M^+), 253, 187, 175, 174 (100), 161, 146, 130, 121, 107, 91, 89, 77.

Further elution of the column with benzene (50 ml × 4) gave dianisalacetone (6.1 g).

Irradiation of **VI** *in cyclohexane*

A solution of **VI** (0.5 g) in dry cyclohexane (250 ml) was irradiated for 6 hr as in the case of **IIa**. Removal of solvent under reduced pressure afforded a gummy material which was crystallised from hexane-benzene (1 : 4), yield 0.4 g, m.p. 139-40°; homogeneous on TLC (R_f: 0.32, benzene) (Found: C, 76.39%; H, 6.8%. $C_{40}H_{40}O_6$ requires C, 77.9; H, 6.49%); IR: 1680, 1610, 1520, 1460, 1180, 1115, 1090 and 1040 cm^{-1}; ^{1}H NMR: δ 1.02-1.42, 1.50-1.80, 1.85-2.15 & 2.30-2.70 (ms, cyclopropane ring Hs), 3.50-3.75 (cyclobutane ring Hs), 3.72 & 3.75 (singlets, 3H, each 2 × OCH_3), 6.60-7.40 (m, arom. Hs); ^{13}C NMR: δ 207.6, 128.3, 128.1, 127.3, 113.9, 55.3, 52.8, 51.7, 47.6, 46.4, 31.3, 31.0, 29.5, 28.9 & 19.1; Mass: m/z 616 (5, M^+), 496, 376, 308, 254, 253, 241, 240, 225, 175, 174, 160, 145, 120, 77, 76 & 55.

7-Phenyl-3-benzylidenespiro[2.5]*octan-2-one* (**IXa**)

2,6-Dibenzylidenecyclohexanone (**VIIIa**) was prepared by condensing cyclohexanone (9.8 g) with benzaldehyde (22 g) in the presence of NaOH (25 g) in EtOH (200 ml) and H_2O (200 ml). A light yellow solid was obtained which was washed thoroughly with H_2O and crystallized from EtOAc, yield 24 g; m.p. 115-16°; IR: 1660 cm^{-1}; ^1H NMR: δ 1.67-1.86 (m, 2H), 2.8-2.95 (t, 4H), 7.27-7.44 (m, arom. Hs), 7.79 (s, 2H, benzylic Hs).

VIIIa (13.5 g) in DMSO (50 ml) was reacted with dimethyloxosulphoniummethylide [obtained from reaction of trimethyloxosulphonium iodide (3 g) with NaH (0.66 g) in DMSO (15 ml)] at ambient temperature. After stirring overnight, the contents were poured into ice cold water and extracted with CH_2Cl_2 (50 ml × 4). The extract was washed thoroughly with H_2O and dried (Na_2SO_4). Removal of solvent gave a yellow oil which was chromatographed over silica gel (100 g in hexane). Elution with hexane-benzene (2 : 3, 50 ml × 4) gave **IXa** as a light yellow oil which crystallised from hexane-benzene (1 : 4), yield 2.0g; m.p. 95-96°; UV: 298 nm; IR: 1665, 1600, 1460, 1180, 1150, 1110, 1065 & 1040 cm^{-1}; ^1H NMR: δ 1.22-1.34 (dd, 1H, cyclopropane H), 1.49-1.66 (m, 4H), 1.87-2.00 (dd, 1H), 2.85-3.05 (m, alicyclic Hs), 6.10-7.78 (m, arom. and olefinic-Hs); ^{13}C NMR: δ 200.8, 136.9, 135.2, 130.3, 129.2, 128.4, 128.2, 128.0, 126.6, 36.7, 35.5, 29.0, 27.3, 22.9 & 22.5; Mass: m/z 289 (90, $M^+ + 1$), 288 (100, M^+), 287, 260, 245, 117, 116, 115, 103, 91 and 77.

Further elution with benzene (50 ml × 60) gave **VIIIa** (8 g, m.p., m.m.p., & IR).

7-p-Methoxyphenyl-3-p-methoxybenzylidenespiro[2.5]*octan-2-one* (**IXb**)

2,6-Di-*p*-anisylidenecyclohexanone (**VIIIb**) was obtained by condensing cyclohexanone (9.8 g) with anisaldehyde (27.6 g) in presence of NaOH (25 g) in EtOH (250 ml) and H_2O (200 ml) mixture. The obtained yellow solid was washed with water and crystallised from hot EtOH, yield 30 g; m.p. 158-59°; IR: 1660 cm^{-1}; ^1H NMR: δ 7.75 (s, 2H, benzylic Hs), 7.43 (d, 4H, J = 9 Hz, arom. Hs), 6.91 (d, 4H, J = 9 H, arom. Hs), 3.82 (s, 6H, 2 × OCH_3), 2.9 (t, 4H), 1.90-1.71 (m, 2H).

VIIIb (3.8 g) in DMSO (50 ml) was reacted with dimethyloxosulphonium methylide [generated from trimethyloxosulphonium iodide (1 g), NaH (0.22 g) in DMSO (10 ml)], as described elsewhere in the paper. The crude product was chromatographed over silica gel (30 g in benzene). Elution with benzene (50 ml × 30) gave **IXb** as a light yellow oil, which crystallised from hexane-benzene (1 : 4), yield 1.2 g, m.p. 105-6°; UV: 325 nm; IR: 1660, 1090, 1040 and 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12-1.28 (dd, 1H, cyclopropane H), 1.4-1.72 (t, 4H), 1.84-2.08 (dd, 1H, cyclopropane H), 2.80-3.0 (m), 6.80-7.64 and olefinic-Hs); ^{13}C NMR: δ 200.8, 159.7, 158.1, 135.5, 133.2, 132.3, 130.3, 129.0, 128.5, 113.8, 113.5, 55.2, 36.4, 35.4, 24.2, 27.3, 23.0 & 22.5; Mass: m/z 348 (100, M^+), 298, 284, 199, 173, 147, 143, 135, 121, 105, 91, 87, 77 and 74.

Irradiation of **IXa** *in benzene*

A solution of **IXa** (0.5 g) in thiophene-free dry benzene (250 ml) was irradiated under N_2 atmosphere for 6 hr as described for **IIa**. The solvent was removed under reduced pressure and the crude yellow oil was chromatographed on silica gel (15 g in hexane). Elution with hexane-benzene (2 : 3, 40 ml × 10) furnished **Xa** as a light yellow oil (0.26 g) which gave a single spot on TLC. (R_f : 0.38 benzene); IR: 1670, 1610, 1595, 1170, 1150, 1110, and 1040 cm^{-1}; ^1H NMR: δ 1.20-1.33 (dd, 1H, cyclopropane Hs), 1.37-1.73 (m, 4H), 1.83-1.97 (dd, 1H), 2.60-2.70 (m, alicyclic-Hs), 6.57 (1H, olefinic-H), 7.08-7.60 (arom. Hs); ^{13}C NMR: δ 201.1, 136.9, 136.1, 135.0, 130.2, 128.9, 127.9, 127.4, 126.5, 35.1, 34.8, 27.1, 23.3 & 19.8; Mass: m/z 288 (90, M^+), 287, 260, 245, 183, 169, 154, 143 (100), 141, 130, 128.

Further elution with benzene (40 ml × 5) yielded **IXa** 0.085 g (m.p., m.m.p., IR, ^1H NMR).

Irradiation of **IXb** *in benzene*

A solution of **IXb** (0.5 gm) in thiophene-free dry benzene (250 ml), was irradiated for 6 hr as described for **IIa**. The obtained yellow oil was loaded onto 8 silica gel G-coated preparative layer plates which were developed with benzene (three runs). Two components thus separated were identified as **IXb** (0.085 g, m.p., m.m.p., R_f: 0.46, benzene) and **Xb** (0.12 g, R_f: 0.44, benzene); IR (neat): 1665, 1660, 1520, 950 cm^{-1}; ^1H NMR: δ: 1.16-1.26 (dd, cyclopropane H), 1.46-1.69 (m, 4H), 1.80-1.98 (dd, 1H, cyclopropane H), 2.65-2.9 (t), 3.69 and 3.73 (s, 3H each, 2 × OCH_3), 6.24 (s, 1H, C_1'-H), 6.80-7.64 (m, arom. Hs); ^{13}C NMR: δ 197.5, 134.4, 130.8, 113.3, 112.8, 55.0, 39.1, 37.8, 36.4, 29.8, 25.3, 23.7 & 19.6; Mass: m/z 348 (100, M^+), 237, 199 (100), 184, 173, 171, 159, 147, 145, 121, 115, 91.

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Studies on thiasteroids: Part II*—Investigations concerning the total syntheses of 12-thiasteroids, 2,6-bisthiabenz[3,4]estra-3,5(10),8,14-tetraen-17-one and its D-homo analogue and 2,6,16-tristhiabenz[3,4]-D-homoestra-3,5(10),8,14-tetraen-17a-one

S R Ramadas* & S Kumaresan
Department of Chemistry, Indian Institute of Technology, Madras 600 036

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Syntheses of 12-thia-C-secosteroids starting from N-(1-naphthylmethylthio)succinimide (I) as well as the synthesis of racemic 2,6-bisthiabenz[3,4]estra-3,5(10)-8,14-tetraen-17-one (XI), its D-homo analogue(XIII) and 2,6,16-tristhiabenz[3,4]-D-homoestra-3,5(10)-8,14-tetraen-17a-one (XV) from 1-oxo-4,9-bisthia-1,2,3,4,9,10-hexahydrophenanthrene (VII) are described.

In view of our interest[1] in the area of 12-thiasteroids, we report, herein, the syntheses of a few 12-thia-C-secosteroids and their cyclodehydration leading to the formation of 12-thiasteroid skeleton (Scheme 1).

The thiosuccinimide derivative (I)[1] was condensed with 2-ethoxycarbonylcyclopentanone[2] under the influence of 'Triton-B' in benzene to furnish the anticipated 13-ethoxycarbonyl-12-thia-8,14-secogona-1,3,5(10)-6,8-pentaen-14-one (II) as a light pale yellow gunm, which failed to crystallize, in 67% yield. Attempted cyclodehydration of II employing protonic and Lewis acids as catalysts failed to furnish the expected gonane derivative (III). It may be pointed out that lack of electron donating group in the appropriate position in the naphthalenic moiety might be responsible for the observed failure in effecting cyclodehydration.

It was also felt that with a more easily enolizable 1,3-diketone, if present as a D-ring in the C-secosteroid, cyclodehydration would be facile. With this end in view, the preparation of IV was undertaken. Thus the thiosuccinimide derivative (I) was condensed with dimedone[3] using 'Triton-B' to afford 16, 16-dimethyl-12-thia-D-homo-8, 14-secogona-1,3,5(10),6,8,13-hexaen-17a-one-14-ol (IV) as a colourless solid in 74% yield. Compound IV exists entirely in the enol form in polar solvents like $CHCl_3$. This is evident from its IR, PMR and CMR spectral data. Most surprisingly compound IV also resisted cyclodehydration to give the expected VI in the presence of protonic and Lewis acids as catalysts.

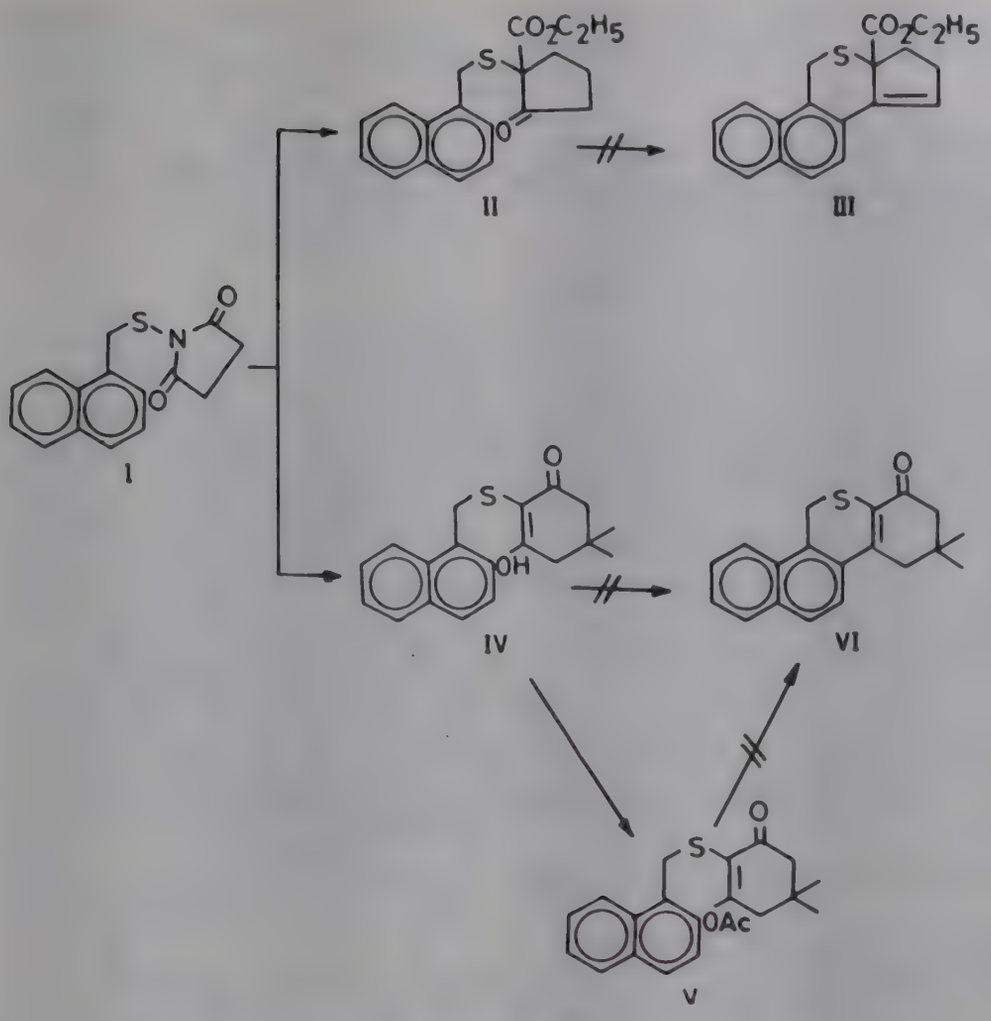
Alternatively, IV was converted into 16,16-dimethyl-12-thia-D-homo-8, 14-secogona-1, 3, 5(10)-6,8,13-hexaene-17a-one-14-acetate (V). Compound V, which was obtained as a thick yellow gum in 92% yield, also failed to undergo cyclodehydration in refluxing acetic anhydride. It was recovered unchanged. The failure of V to undergo cyclodehydration to furnish the expected VI was rather unexpected.

A careful survey of literature reveals that no report is available on the total synthesis 2,6-bisthia- and 2,6-16-tristhia pentacyclic steroids. In view of this and in view of our interest[4,5] in the synthesis of newer types of thiasteroids, we report, herein, the total synthesis of the racemates of the compounds XI, XIII and XV (Scheme 2).

The starting ketone, 1-oxo-4,9-bisthia-1,2,3,4,9,10-hexahydrophenanthrene (VII), prepared from thiochroman-4-one[6], on treatment with vinylmagnesium bromide under Normant reaction conditions[7] afforded the anticipated, 1-hydroxy-4,9-bisthia-1-vinyl-1,2,3,4,9,10-hexahydrophenanthrene (VIII) which was highly unstable. Compound VIII was immediately converted into the more stable 4,9-bisthia-1,2,3,4,9,10-hexahydrophenanthrenylideneethyl isothiuronium acetate (IX) by treatment with thiourea and glacial acetic acid[8]. Condensation of IX with 2-methylcyclopentane-1,3-dione in refluxing aqueous ethanol (50%, v/v) gave 8,14-seco-2,6-bisthiabenz[3,4]estra-3,5(10),9(11)-trien-14,17-dione (X), which on cyclodehydration using methanolic hydrochloric acid[9] afforded the racemic 2,6-bisthiabenz[3,4]estra-3,5(10),8,14-tetraen-17-one (XI).

Condensation of IX with 2-methylcyclohexane-

†The earlier publication on this subject (i.e. vide Ref. 1) is treated as Part I.



Scheme 1

1,3-dione[10] under the aforementioned conditions yielded, 8,14-seco-2,6-bisthiabenz[3,4]-D-homoestra-3,5(10),9(11)-trien-14,17a-dione (XII) which on cyclodehydration as above gave the racemic 2,6-bisthiabenz[3,4]-D-homoestra-3,5(10),8,14-tetraen-17a-one (XIII).

In a similar fashion, condensation of IX with 2-methyl-5-thiacyclohexane-1,3-dione[11] in refluxing aqueous ethanol (2:5 water-ethanol, v/v) afforded 8,14-seco-2,6,16-tristhiabenz[3,4]-D-homoestra-3,5(10),9(11)-trien-14,17a-dione (XIV). Cyclodehydration of XIV as above gave XV, albeit in very poor yield. However cyclodehydration of XIV using PTS in refluxing benzene furnished the expected XV in better yield.

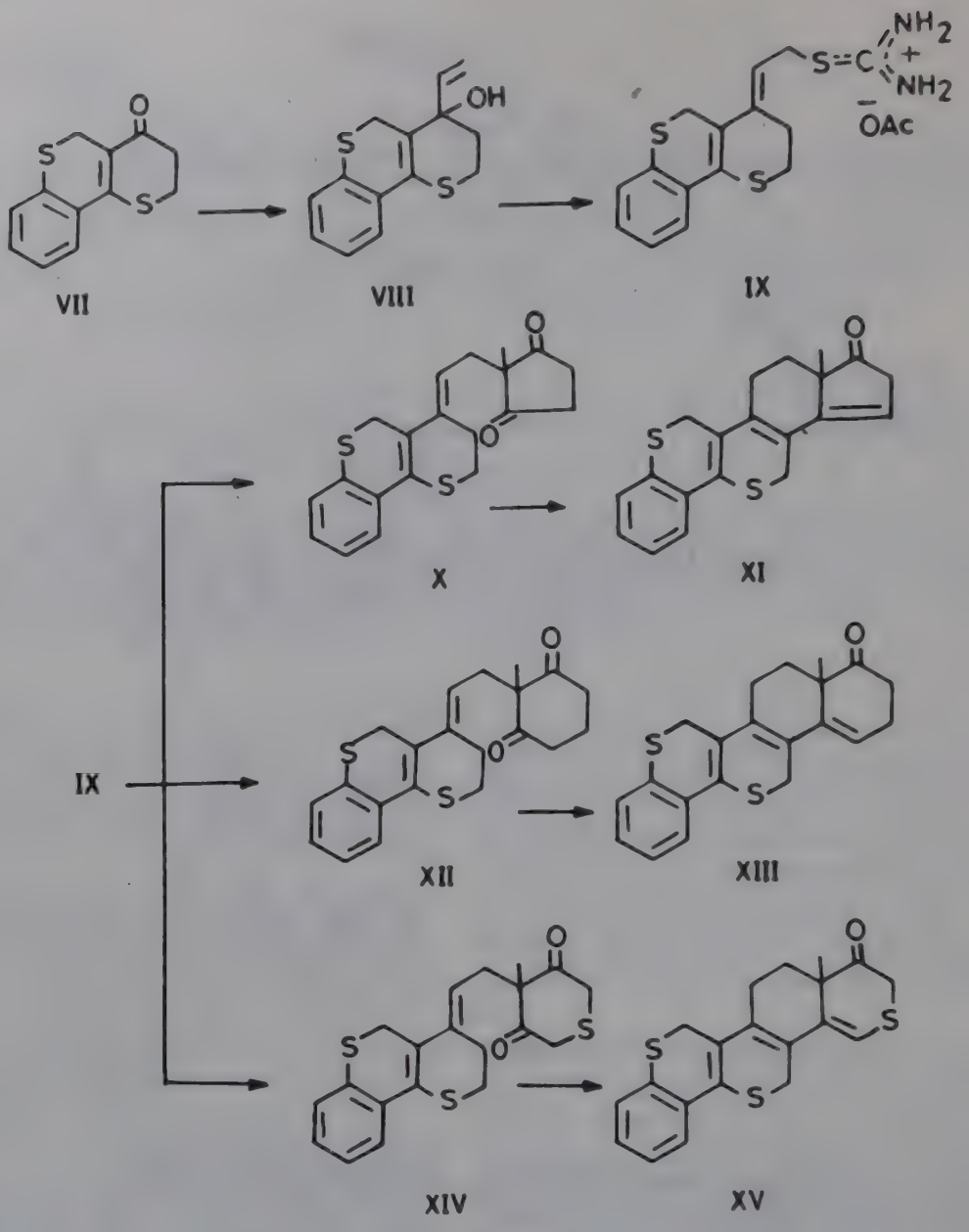
Attempted catalytic hydrogenation of 8,9- and 13,15-olefinic bonds in XI and XIII over 10% Pd/C was unsuccessful probably due to poisoning of sulphur present in these compounds. Initial screening of the bisthiasteroid (XIII) for biological activity showed prominent antitumor activity against fibrosarcoma in rats.

Experimental Procedure

All melting points are uncorrected. Petroleum ether used had the b.p. 60-80°. IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, model 257; PMR spectra, on a Varian EM-390 spectrometer operating at 90 MHz using TMS as internal standard and mass spectra, on a DS-55 instrument. CMR data were obtained by a study of the proton-noise decoupled as well as off-resonance spectra.

13-*Ethoxycarbonyl*-12-*thia*-8,14-*secogona*-1,3,5(10),6,8-*pentaen*-14-*one* (*II*)

To a stirred solution of 2-ethoxycarbonylcyclopentanone[2] (1.56 g) in dry benzene (50 ml) and dry *t*-butanol (2 ml) at room temperature was added Triton-B (a few drops in one lot). Stirring was continued for further 30 min. To this, the thiosuccinimide derivative (I) (2.71 g) in benzene (20 ml) was added in one lot with stirring. Stirring was continued for 48 hr, water (20 ml) added, the organic layer washed with water (3 × 20 ml) and dried (Na_2SO_4). Evapor-



Scheme 2

ation of the solvent afforded a thick gum (2.5 g), which was chromatographed over silica gel (120 g). Elution with benzene-hexane (1:1) (1000 ml) gave the analytically pure sample of II (2.2 g) as a pale yellow gum in 67% yield; IR(neat): 1740-1720 cm^{-1} ($\nu C=O$); PMR($CDCl_3$): δ 1.2 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 1.4-2.2 (m, 6H, methylene protons at C-15, C-16 and C-17), 4.0 (q, 2H, $-COOCH_2CH_3$; J = 7 Hz), 4.1 (s, 2H, methylene at C-11) and 7.0-7.9 (m, 7H, Ar); CMR($CDCl_3$): δ 14.23 (q, $-COOCH_2CH_3$), 22.58 (t, C-16), 30.62 (t, C-17), 33.72 (t, C-11), 46.55 (t, C-15), 51.81 (s, C-13), 61.40 (t, $-COOCH_2CH_3$), 124.97-135.1 (aromatic carbons), 173.23 (s, $-COOCH_2CH_3$) and 174.46 (s, carbonyl carbon at 14); MS: m/z 328 ($M^{+\cdot}$, 2%) (Found: C, 69.3; H, 5.9. $C_{19}H_{20}O_3S$ requires C, 69.5; H, 6.1%).

16,16-*Dimethyl*-12-*thia*-*D*-*homo*-8,14-*secogona*-1,3,5(10),6,8,13-*hexaen*-17*a*-*one*-14-*ol* (*IV*)

The thiosuccinimide derivative (I) (2.71 g) was treated with dimedone[3] (1.4 g) following the conditions described for II. Stirring was continued for 48 hr. Work-up of the reaction mixture furnished a thick gum (2.6 g) which was chromatographed over silica gel (150 g). Benzene-hexane (1:1) eluates afforded a white gum which on trituration with chloroform gave a colourless solid. Recrystallization of this solid from chloroform-hexane furnished analytically pure sample of IV (2.3 g) as a white crystalline solid, m.p. 94-95°, in 74% yield; IR($CHCl_3$): 3700-3100 (br, enolic-OH) and 1650 cm^{-1} (conjugated carbonyl); PMR($CDCl_3$): δ 0.9 (s, 6H, gem-dimethyl), 2.0 (s, 2H, C-15 methylene), 2.2 (s, 2H, C-17 methylene), 4.1 (s, 2H, $Ar-CH_2-S$), 4.4 (br, enol-

ic-OH, disappeared with D_2O) and 6.8-7.9 (m, 7H, Ar); CMR($CDCl_3$): δ 28.46 (q, gem-dimethyl), 31.24 (s, C-16), 35.57 (t, C-15), 42.07 (t, C-11), 51.66 (t, C-17), 106.41 (s, C-13), 124.66-135.18 (aromatic carbons and C-14) and 179.4 (s, conjugated carbonyl carbon at 17a); MS: m/z 312 ($M^{+\cdot}$, 5%) (Found: C, 73.4; H, 6.2. $C_{19}H_{20}O_2S$ requires (C, 73.1; H, 6.4%).

16,16-*Dimethyl*-12-*thia*-*D*-*homo*-8,14-*secogona*-1,3,5(10),6,8,13-*hexaen*-17*a*-*one*-14-*acetate* (*V*)

A mixture of the secogonane (IV) (1.56 g), acetic anhydride (1 ml) and dry pyridine (1.5 ml) was kept at 100° with stirring for 3 hr. Excess reagents were removed under reduced pressure to obtain a thick gum which on column chromatography over silica gel (90 g) gave from benzene-hexane (1:1) eluates, analytically pure V as a thick yellow gum (1.62 g) in 92% yield. Attempted solidification of this gum was unsuccessful; IR(neat): 1760(enol-ester) and 1670 cm^{-1} (α,β-unsaturated carbonyl); PMR($CDCl_3$): δ 0.9 (s, 6H, gem-dimethyl), 1.8 (s, 3H, $-OCOCH_3$), 2.2 (s, 2H, C-15 methylene), 2.3 (s, 2H, C-17 methylene), 4.2 (s, 2H, C-17 methylene), 4.2 (s, 2H, $Ar-CH_2-S$) and 7.0-8.1 (m, 7H, Ar) (Found: C, 71.0; H, 6.5. $C_{21}H_{22}O_3S$ requires C, 71.2; H, 6.2%).

1-*Hydroxy*-4,9-*bisthia*-1-*vinyl*-1,2,3,4,9,10-*hexahydrophenanthrene* (*VIII*)

To a precooled (−20°) stirred suspension of vinylmagnesium bromide (from 20 ml of vinylbromide and 3.5 g magnesium turnings) in dry tetrahydrofuran (THF) (50 ml) was added dropwise, under nitrogen atmosphere, a precooled (−20°) solution of VII (4.68 g) in dry THF (40 ml). The reaction mixture was brought to room temperature during 2 hr and then refluxed for 4 hr. The dark brown Grignard complex was decomposed by adding ice-cold saturated ammonium chloride solution and extracted with ether (3 × 100 ml). The ethereal layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give crude VIII (5.9 g) as a thick brown gum, which was found to be highly unstable and could not be distilled *in vacuo* (decomposed at 105-10°/3×10^{-4} mm). The crude product on rapid chromatography over neutral alumina (120 g) gave from benzene eluates (500 ml) a fairly pure sample of the vinyl carbinol (VIII) as a thick brown gum (4.45 g) in 85% yield; IR(neat): 3600-3100 (br, H-bonded), 1620 (C=C), 1570, 1450 (aromatic skeletal vibrations), 990 and 920 cm^{-1} (vinyl); PMR($CDCl_3$): δ 2.0 (m, 2H, S-CH_2-CH_2), 2.7 (m, 2H, S-CH_2-CH_2), 3.0 (s, 1H, −OH, disappeared with D_2O), 3.11 (A) and 3.21 (B) [(q, 2H (AB-quartet)], J_{AB} = 14 Hz, CH_2 at C-10), 4.8-5.8 (m, 3H, vinyl protons, ABC pattern) and 6.7-7.5 (m, 4H, Ar) (Found: C, 64.0; H, 5.2. $C_{14}H_{14}OS_2$ requires C, 64.1; H, 5.3%).

4,9-*Bisthia*-1,2,3,4,9,10-*hexahydrophenanthrenylideneethylisothiuronium acetate* (*IX*)

To a precooled (0-5°), stirred mixture containing purified VIII (4 g) and thiourea (1.2 g), was added glacial acetic acid (12 ml). The resulting mixture was brought to room temperature during 2-3 hr and stirring continued for 12 hr. Dry ether (80 ml) was slowly added to the reaction mixture and the precipitated solid filtered and washed with dry acetone (5 × 10 ml) to furnish the pure IX (4.4 g, 76%) as a white amorphous solid, m.p. 136-38°; IR(KBr): 3200 (br, ν_{NH}), 1560 and 1410 cm^{-1} (acetate anion); PMR(DMSO-d_6): δ 1.8 (s, 3H, $-OCOCH_3$), 2.6-3.1 (m, 4H, CH_2 at C-2 and C-3), 3.5 (s, 2H, CH_2 at C-10), 3.8 [d, 2H, J = 8 Hz, CH_2-S-$C(NH_2)_2$], 5.7 (t, 1H, J = 8 Hz, olefinic H) and 6.8-7.5 (m, 4H, Ar); MS: m/z (%), 244(12), 243(8), 212(5), 211(10), 76(57), 60(50) and 43(65) (Found: C, 54.0; H, 5.7. $C_{17}H_{20}O_2N_2S_3$ requires C, 53.7; H, 5.3%).

8,14-*Seco*-2,6-*bisthiabenz*[3,4]*estra*-3,5(10),9(11)-*trien*-14-17-*dione* (*X*)

Compound IX (1 g) and 2-methylcyclopentane-1,3-dione[12] (0.3 g) were refluxed in 50% aq. ethanol (100 ml) for 5 hr. After the removal of the solvent under reduced pressure, the residue was extracted with ether (4 × 30 ml). The combined ether extract was washed successively with saturated aq. sodium bicarbonate (2 × 25 ml) and aq. sodium chloride (2 × 20 ml). The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow gum (0.86 g) which on column chromatography over silica gel (50 g) afforded from benzene-hexane (1:1) eluates (300 ml), pure X (0.76 g, 81%) as a light yellow gum. Attempts towards solidification of this gum were, however, unsuccessful; IR(neat): 1760 and 1720 (characteristic of 2,2-disubstituted cyclopentane-1,3-dione)[13], 1550, 1440 and 1410 cm^{-1} (aromatic C=C); PMR($CDCl_3$): δ 1.1 (s, 3H, C-18 methyl), 2.45 (d, 2H, J = 8 Hz, CH_2 at C-12), 2.60 (s, 4H, methylenes at C-15 and C-16), 2.7-3.0 (m, 4H, methylenes at C-7 and C-8), 3.3 (s, 2H, CH_2 at C-1), 5.3 (t, 1H, J = 8 Hz, olefinic H at C-11) and 6.8-7.4 (m, 4H, Ar); MS: m/z 356 ($M^{+\cdot}$) (Found: C, 67.2; H, 5.5. $C_{20}H_{20}O_2S_2$ requires C, 67.4; H, 5.6%).

2,6-*Bisthiabenz*[3,4]*estra*-3,5(10)-8,14-*tetraen*-17-*one* (*XI*)

To a solution of X (0.46 g) in methanol (40 ml) was added dropwise with stirring, conc. hydrochloric acid until the solution became turbid and turbidity

persisted. The reaction mixture was stirred for further 15 min under cooling. The precipitate was filtered off and washed with water. Rapid chromatography of crude solid (0.44 g) over silica gel (25 g) furnished from benzene-hexane (1:3) eluates (250 ml) a greenish yellow solid which was recrystallized from hexane-chloroform to afford pure XI (0.37 g, 85%) as a greenish yellow solid, m.p. 150-52°; IR(KBr): 1735 cm^{-1} (C=O); PMR($CDCl_3$): δ 1.1 (s, 3H, C-18 methyl), 1.4-3.35 (m, 8H, methylenes at C-6, C-11, C-12 and C-16), 3.4 (s, 2H, CH_2 at C-1), 5.7 (t, 1H, J = 3 Hz, olefinic H) and 6.8-7.5 (m, 4H, Ar); CMR($CDCl_3$): δ 20.5 (q, C-18 methyl), 24.9 (t, C-11), 25.4 (t, C-7), 26.7 (t, C-12), 27.4 (t, C-1), 42.1 (t, C-16), 48.8 (s, C-13), 116.5 (d, C-15), 118.6 (s, C-14), 125.4-145.4 (aromatic carbons) and 218.7 (s, carbonyl carbon at 17); MS: m/z 338 ($M^{+\cdot}$) (Found: C, 70.9; H, 5.3. $C_{20}H_{18}OS_2$ requires C, 71.0; H, 5.3%).

8,14-*Seco*-2,6-*bisthiabenz*[3,4]-*D-homoestra*-3,5(10),9(11)-*trien*,17*a*-*dione* (*XII*)

Condensation of IX (0.95 g) with 2-methylcyclohexane-1,3-dione[10] (0.32 g) as described for X furnished a dark brown gum (0.83 g), which was chromatographed over silica gel (50 g). Elution with benzene-hexane (1:1) (300 ml) gave XII (0.66 g, 71%) as a pale brown gum. All attempts to solidify the gum were unsuccessful; IR(neat): 1725, 1690 (characteristic of 2,2-disubstituted cyclohexane-1,3-dione moiety)[13], 1460 and 1425 cm^{-1} (aromatic skeletal vibrations); PMR($CDCl_3$): δ 1.23 (s, 3H, C-18 methyl), 1.8 (m, 2H, CH_2 at C-16), 2.4-3.0 (m, 10H, methylene protons at C-7, C-8, C-12, C-15 and C-17), 3.3 (s, 2H, CH_2 at C-1), 5.2 (t, 1H, J = 8 Hz, olefinic proton at C-11) and 6.8-7.4 (m, 4H, Ar); MS: m/z 370 ($M^{+\cdot}$) (Found: C, 68.5; H, 6.2. $C_{21}H_{22}O_2S_2$ requires C, 68.1; H, 5.9%).

2,6-*Bisthiabenz*[3,4]-*D-homoestra*-3,5(10),8,14-*tetraen*-17*a*-*one* (*XIII*)

Compound XII (0.25 g) was subjected to cyclodehydration, as described for XI, to obtain XIII as a crude yellow solid (0.21 g). Rapid chromatography of this solid over silica gel (20 g) furnished from benzene-hexane (2:3) eluates (100 ml) almost pure XIII (0.15 g, 63%) as a yellow solid, m.p. 170-71°; IR($CHCl_3$): 1695 (C=O), 1610, 1475, 1445 and 1420 cm^{-1} (aromatic skeletal vibrations); PMR($CDCl_3$): δ 1.2 (s, 3H, C-18 methyl), 1.4-3.0 (m, 8H, CH_2 at C-11, C-12, C-16 and C-17), 3.21(A) and 3.41(B) [q, 2H (AB system), J_{AB} = 15 Hz, CH_2 at C-7], 3.43 (s, 2H, CH_2 at C-1), 5.85 (t, 1H, J = 4.5 Hz, olefinic H) and 6.8-7.5 (m, 4H, Ar); MS; m/z 352 ($M^{+\cdot}$) (Found: C, 71.2; H, 5.8. $C_{21}H_{20}OS_2$ requires C, 71.6; H, 5.7%).

8,14-*Seco*-2,6,16-*tristhiabenz*[3,4]-*D-homoestra*-3,5(10),9(11)-*trien*-14,17*a*-*dione* (*XIV*)

A mixture of IX (1.14 g) and 2-methyl-5-thiacyclohexane-1,3-dione[11] (0.47 g) was refluxed in aq. ethanol (2:5 water-ethanol mixture, 70 ml) for 15 min and the reaction mixture worked up as in the case of X to get a light brown gum (1 g, 86%). No attempt was made to purify this material because of its decomposition at room temperature. The crude sample was immediately used for the next step; IR(neat): 1725 and 1690 (due to 2,2-disubstituted cyclohexane-1,3-dione)[13], 1610, 1460 and 1430 cm^{-1} (aromatic skeletal vibrations); PMR($CDCl_3$): δ 1.3 (s, 3H, C-18 methyl), 2.5-3.0 (m, 6H, CH_2 at C-7, C-8 and C-12), 3.3 (s, 4H, CH_2 at C-15 and C-17), 3.35 (s, 2H, CH_2 at C-1), 5.3 (t, 1H, J = 8 Hz, olefinic H) and 6.8-7.5 (m, 4H, Ar).

2,6,16-*Tristhiabenz*[3,4]-*D-homoestra*-3,5(10),8,14-*tetraen*-17*a*-*one* (*XV*)

A solution of XIV (0.5 g), in dry, thiophene-free benzene (50 ml) containing PTS (0.05 g) was refluxed for 15 min using a Dean-Stark water trap. The reaction mixture was cooled and poured into ice-cold water (40 ml). The organic layer was separated, the aqueous layer extracted with benzene (2 × 20 ml), the combined benzene extract washed successively with saturated aq. sodium bicarbonate (2 × 20 ml) and sodium chloride (2 × 15 ml) solutions and dried (Na_2SO_4). Evaporation of the solvent yielded a crude brown gum (0.41 g) which on rapid chromatographic purification over silica gel (20 g) furnished from benzene-hexane eluates (100 ml) a pale yellow solid. This solid on recrystallization from hexane-methylene chloride afforded analytically pure XV (0.31 g, 65%) as pale yellow crystalline solid, m.p. 167-69°; IR($CHCl_3$): 1700 (C=O), 1610, 1460, 1430 and 1410 cm^{-1} (aromatic skeletal vibrations); PMR($CDCl_3$): δ 1.3 (s, 3H, C-18 methyl), 1.7-2.7 (m, 4H, CH_2 at C-11 and C-12), 3.2 (s, 2H, S-CH_2-CO), 3.18(A) and 3.31(B) [q, 2H (AB system), J_{AB} = 15 Hz, CH_2 at C-7], 3.34 (s, 2H, CH_2 at C-1), 6.1 (s, 1H, olefinic H) and 6.8-7.4 (m, 4H, Ar); MS: m/z 370 ($M^{+\cdot}$) (Found: C, 64.7; H, 4.7. $C_{20}H_{18}OS_3$ requires C, 64.9; H, 4.9%).

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A novel one-pot synthesis of 8-acetoxymethylisolongifolene and 8-acetoxymethylcycloisolongifolene from longifolene†

U R Nayak*, V B Deodhar & V S Dalavoy
National Chemical Laboratory, Pune 411 008

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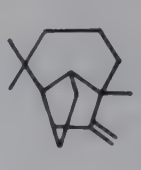
Boron trifluoride etherate-induced dual catalysis of the rearrangement of longifolene (**1**) to isolongifolene (**2**) and a concomitant formaldehyde addition to **2** in acetic acid medium is achieved in a one-pot reaction to give a mixture of 8-acetoxymethylisolongifolene (**3**) and 8-acetoxymethylcycloisolongifolene (**4**), not separable by chromatography. On hydrolysis of the acetate mixture followed by Jones' oxidation of the resultant alcohols **6** and **7**, only the former generates the aldehyde **8** while the latter yields the acid **9**. Lithium aluminium hydride reduction of **8/9** back to the parent alcohols **6/7** followed by acetylation enables preparation of the pure acetates **3/4** by a chemical method.

While formaldehyde adds[1] on to longifolene (**1**) in acetic acid medium in the absence of any catalyst, isolongifolene (**2**) does so only in the presence of an acid catalyst. In a patent[2], it has been reported that **2** on heating with paraformaldehyde, acetic acid and sulphuric acid (catalyst) at 60°, gives a mixture (not separated) of two perfumery chemicals, 8-acetoxymethylisolongifolene (**3**) and 8-acetoxymethylcycloisolongifolene (**4**). We now describe an innovative route for the synthesis of **3** and **4** (mixture) directly from the naturally occurring **1** (instead of its isomer **2**) in a one-pot reaction; this strategy envisages a unique BF_3 etherate-induced dual catalysis of the rearrangement of **1** and **2** with concomitant addition of formaldehyde to the latter (in acetic acid medium) to give the acetates **3** and **4**. Furthermore, a novel chemical method for the separation of **3** and **4** (from the chromatographically inseparable mixture) and their spectral characterization are also reported.

Treating a benzene solution of longifolene (**1**) with BF_3 etherate as catalyst at ambient temperature for 3 hr completely transformed[3] it into isolongifolene (**2**). Without any workup the mixture was reacted as such with paraformaldehyde in acetic acid by refluxing for 6 hr when the Lewis acid-catalyzed Prins reaction[4] on **2** took place smoothly. On fractional distillation of the product a mixture of **3** and **4** was obtained in 50% yield after a fore-run of unreacted olefin (i.e. **2**); GLC of the mixture indicated 33% of **3** and 54% of **4**. Mechanistically, formation of the allylic acetate (**3**) cyclopropyl acetate (**4**) can be easily rationalized from **2** (formed *in situ* by the BF_3-induced rearrangement of **1**) which further reacts with the activated positive species $^{(+)}CH_2OAc$ also present in the medium to generate the C-7 carbocation **5**, a progenitor to the two neutral compounds **3** and **4** as shown in Scheme 1. Although the mixture (**3** + **4**) has not been separated earlier[2] and could not be resolved even now by column chroamtography over silica gel, it has, however, been possible to prepare pure **3** and **4** indirectly by a chemical approach. When the mixture of



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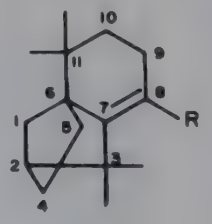
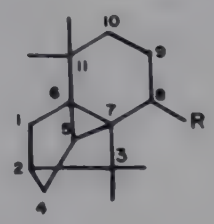
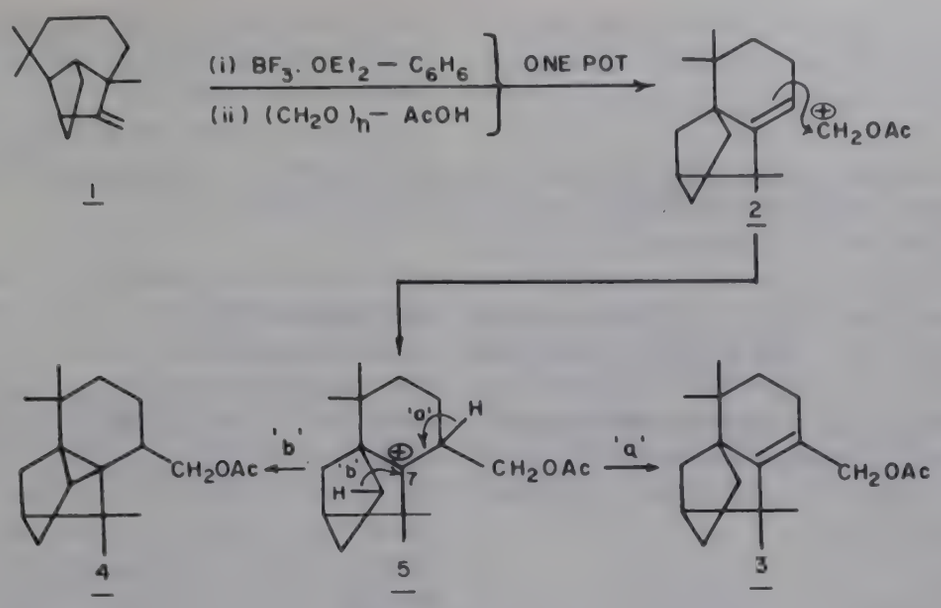


2 : R = H
3 : R = CH_2OAc
6 : R = CH_2OH
8 : R = CHO



4 : R = CH_2OAc
7 : R = CH_2OH
9 : R = CO_2H

†NCL Communication No. 4263



SCHEME 1

alcohols **6** and **7**, resulting from hydrolysis of the acetates mixture, was treated with Jones' reagent, the allylic alcohol **6** was oxidized to the conjugated aldehyde **8** which could be cleanly separated from the tetracyclic acid **9** resulting from **7**. The presence/absence of a tetrasubstituted double bond in **8/9** is clearly borne out from their carbon-13 NMR spectral data (*vide Experimental*). Reduction of **8/9** back to the parent alcohol **6/7** followed by acetylation afforded pure **3** and **4**. The distinguishing feature in the PMR spectrum of **3** is a 2H singlet at δ 4.53 (CH_2OAc) and a deshielded tertiary methyl singlet at 1.20 while in **4** the acetoxymethylene moiety appears as a multiplet betwen 3.43 and 4.03 ppm. The PMR spectrum of the mixture of **3+4** described earlier was in fact a summation of the proton spectral data of pure **3** and **4**.

Experimental Procedure

Solvent extracts were dried over anhydrous Na_2SO_4. IR spectra (ν_{max} in cm^{-1}) were recorded as smears (liquids) or nujol mulls (solids) on a Pye-Unicam SP-3 IR spectrophotometer; PMR spectra on a Varian T-60 spectrometer; mass spectra on a CEC spectrometer model 21-110B using an ionizing voltage 70 eV and a direct inlet system; and CMR spectra in $CDCl_3$ on a 22.63 MHz Bruker Spectrospin instrument. GLC was carried out employing 3% OV-1 as the stationary phase (temp. 205°, N_2 carrier gas and FID detector).

One-pot synthesis of acetates mixture **3/4** *from longifolene* (**1**)

A solution of **1** (100 g) in benzene (125 ml), to which $BF_3.OEt_2$ (5 ml) was added and kept at 26° for 3 hr, was treated with paraformaldehyde (18 g) and AcOH (100 ml) and refluxed for 6 hr. The mixture was diluted with water, the organic layer was separated and the aqueous phase further extracted with benzene. The combined extract was washed successively with 5% aq. $NaHCO_3$, brine, dried, solvent removed and the residue fractionally distilled: Fr. 1, b.p. 90°/2 mm, hydrocarbon (isolongifolene **2**, 16 g). Fr. 2, b.p. 100-120°/2 mm, mixture (6 g). Fr. 3, b.p. 130-35°/2 mm (**3+4**; 70 g, 50%); PMR (CCl_4): δ 4.53 (s, CH_2OAc of **3**), 1.97 (s, $COCH_3$ of **3** and **4**), 3.43 to 4.03 (m, CH_2OAc of **4**); GLC: **4** (54.4%; RT 4.10 min); **3** (33.1%; RT 4.83 min).

8-*Formylisolongifolene* **8**/8-*carboxycycloisolongifolene* (**9**)

The mixture (**3+4**, 70 g) was treated with 10% aq. alcoholic KOH (500 ml) at room temperature overnight. The mixture was diluted with water, extracted with EtOAc, washed with brine, dried, solvent removed and the residue distilled to furnished a mixture of alcohols **6** and **7**; b.p. 140°/1 mm (65 g). To a cooled and stirred solution of this mixture in acetone (700 ml) was added dropwise Jones' reagent[5] (100 ml) during 0.5 hr. After stirring for another 5 hr, the mixture was diluted with water (1 litre), extracted with EtOAc and separated into acid and neutral parts by washing with 5% aq. KOH (3 × 400 ml). The neutral part was distilled to give **8** as a colourless liquid, b.p. 125°/1 mm (21 g, 33%) which solidified on cooling; m.p. 65°; UV: λ_{max} 260 nm (MeOH, ε = 13360); IR: 2780, 1675, 1640, 1190, 1110, 730. PMR (CCl_4): δ 10.10 (s, 1H, CHO); 1.43, 1.33, 1.00, 0.83 (3H each, four tertiary methyl singlets). CMR (ppm; off-resonance decoupled): 127.9

(s) and 103.0 (s) tetrasubstituted double bond), 192.0 (*d*, HC=O); MS: m/z 232 (M^+, base peak) (Found: C, 82.8; H, 10.5. $C_{16}H_{24}O$ requires C, 82.7; H, 10.4%).

The aqueous alkaline phase was acidified with HCl, extracted with EtOAc, washed with brine, dried, solvent removed and the crude acid (15 g, 22%) was recrystallized from acetonitrile to furnish colourless crystal of **9**, m.p. 125°; IR: 2600 to 3200, 1700, 1420, 1230, 980. PMR (CCl_4): δ 11.60 (bs, 1H, COOH), 1.00, 0.95, 0.90, 0.85 (3H each, four tertiary methyl singlets); CMR (ppm; off-resonance decoupled): 100-180 region transparent; 183.1 (s, O=*C*−OH) (Found: C, 77.5; H, 10.0. $C_{16}H_{24}O$ requires: C, 77.4; H, 9.7%).

LAH reduction of **8**: **6***β*-*acetoxymethylisolongifolene* (**3**)

To a stirred slurry of LAH (0.6 g) in dry ether (30 ml) was added dropwise a solution of **8** (1 g) in ether (40 ml) at room temperature (anhydrous conditions). After stirring for 16 hr the mixture was successively treated with water (1 ml), 15% aq. NaOH (1 ml) and water (3 ml) and stirred for another 15 min. The grannular precipitate was filtered, washed with ether, the filtrate dried, solvent removed and the residue distilled to furnish the alcohol **6** as a colourless liquid, b.p. 160° (bath)/1 mm, which solidified on cooling; m.p. 72°; IR: 3340, 1060, 1010, 990; PMR (CCl_4): δ 3.98 (q, H, CH_2OH, J = 14 Hz); 1.20, 1.10, 0.93, 0.83 (3H each, four tertiary methyl singlets); MS: m/z 234 (M^+) (Found: C, 81.6; H, 11.0. $C_{16}H_{26}O$ requires C, 82.0; H, 11.2%).

Acetylation of **6** with acetic anhydride in pyridine at room temperaure followed by distillation gave the pure acetate **3** as a colourles liquid; IR: 1755, 1250, 1035, 970; PMR (CCl_4): δ 4.53 (s, 2H, CH_2OAc), 1.97 (s, 3H, $COCH_3$), 1.20, 1.10, 0.93, 0.83 (3H each, four tertiary methyl singlets); MS: m/z 276 (M^+) (Found: C, 78.9; H, 10.4. $C_{18}H_{28}O_2$ requires C, 78.2; H, 11.2%).

LAH reduction of acid **9**: **7***β*-*Acetoxymethylcyclo-isolongifolene* (**4**)

To a stirred slurry of LAH (4 g) in dry ether (200 ml) was added dropwise a solution of **9** (8 g) in ether (300 ml) at room temperature. After stirring for 16 hr the mixture was successively treated with water (4 ml), 15% aq. NaOH (4 ml) and water (12 ml) and stirred for 15 min more. The precipitate was filtered and the alcohol **7** was isolated by distillation as a colourless liquid, b.p. 170° (bath)/1 mm (7 g). IR: 3350, 3060, 1050, 1000; PMR (CCl_4): δ 3.33 (bm, 2H, CH_2OH); 1.00, 0.93, 0.87 × 2 (four tertiary methyl singlets); MS: m/z 234 (M^+) (Found: C, 81.4; H, 11.0. $C_{16}H_{26}O$ requires C, 82.0; H, 11.2%).

Acetylation of **7** (Ac_2O-Py) gave the pure acetate **4** as a colourless liquid, b.p. 170° (bath)/1 mm; IR: 3080, 1750, 1245, 1045; PMR (CCl_4): δ 3.43 to 4.03 (m, 2H, HC-CH_2OAc), 1.97 (s, 3H, $COCH_3$), 1.00, 0.97, 0.87, 0.83 (3H each, four tertiary methyl singlets).

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Synthesis of 2,5-dihydro-2,5-diphenylfuran

Ibiba R Jack
Chemistry Department, Rivers State University of Science and Technology, P.M.B. 5080, Port Harcourt, Nigeria

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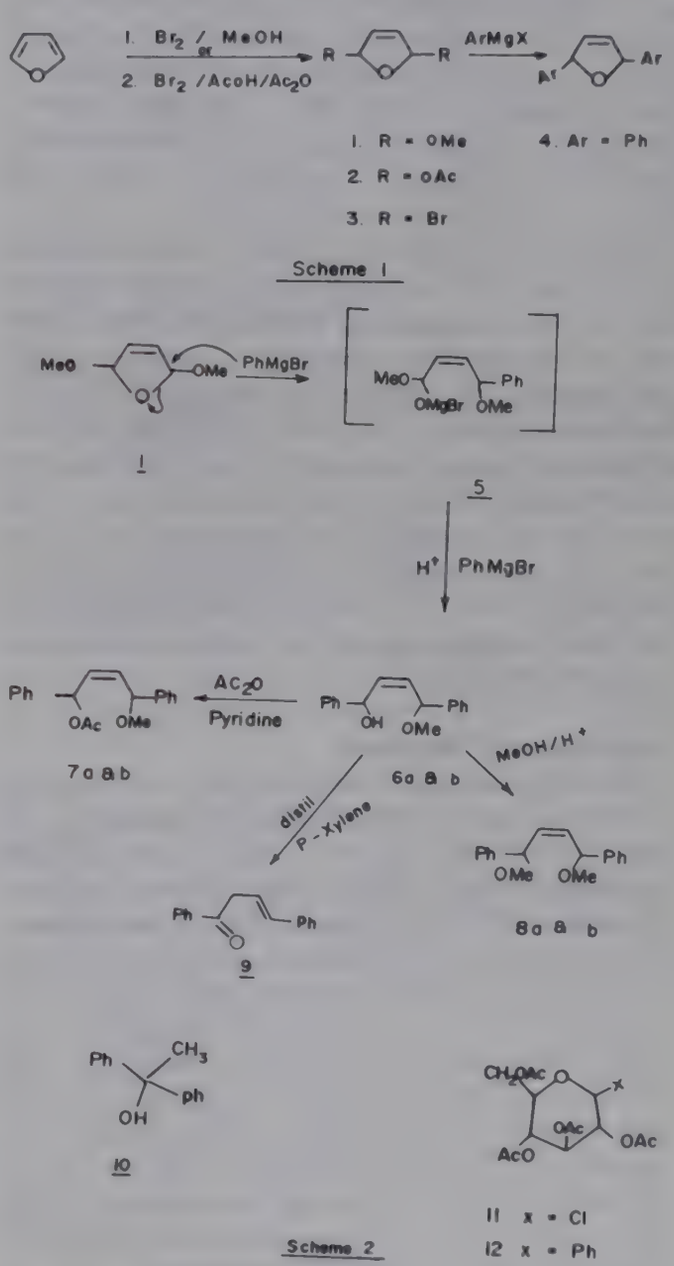
2,5-Dihydro-2,5-diphenylfuran (**4**) has been synthesized by the reaction of phenylmagnesium bromide with 2,5-dibromo-2,5-dihydrofuran (**3**). Reaction of 2,5-dihydro-2,5-dimethoxyfuran (**1**) with phenylmagnesium bromide and phenyllithium however leads to ring opening.

The synthesis of 2,5-diaryl-2,5-dihydrofuran as a synthon became necessary in view of the problems[1] encountered in undertaking the unambiguous synthesis of 2,4-diaryl substituted furofurans[2]. It was hoped that 2,5-diaryl-2,5-dimethoxyfuran (**1**) would readily undergo nucleophilic displacement on treatment with either Grignard reagent or aryllithium to give **4**.

The reaction involved oxidation[3] of furan with bromine in methanol to give **1** (Scheme 1) in 70% yield as a mixture of two isomers. When excess of phenylmagnesium bromide was reacted with one equivalent of **1** in dry diethyl ether at $-78°$ for 2 hr, no reaction was observed. But on allowing the reaction mixture to warm up to room temperature for 4 hr, two spots having R_f 0.69 and 0.53 were observed on TLC. These were isolated by column chromatography as a white crystalline solid, m.p. 73-75° and an oil both of which showed strong OH absorption in their infra red spectra, had identical PMR and mass spectra and were identified as two isomers (**6a** and **6b**) of 1,4-diphenyl-4-methoxy-but-2-en-1-ol (Scheme 2).

The structure was confirmed by spin decoupling and also by acetylation. Irradiation at δ 5.40 caused the OH broad singlet at 3.32 to collapse to a sharp singlet and the multiplet at 5.64-5.76 to a double doublet (J = 2,7 Hz). Also irradiation at δ 5.70 caused the benzylic proton at 5.40 to collapse to a doublet (J = 4 Hz). Acetylation of **6** with acetic anhydride and pyridine gave the acetates (**7a** and **7b**) in which the benzylic protons next to the acetoxy groups were shifted downfield by about δ 1.28 (*vode* experimental). Methylation of the crystalline isomer of the alcohol **6** with methanol and HCl afforded the dimethoxy derivatives (**8a** and **b**). The formation of these isomers (**6a** and **6b**) can be rationalised by suggesting a mechanism involving an initial attack of the Grignard reagent on **1** which results in the formation of a ring opened complex (**5**).



Displacement of the methoxyl by a second phenyl group to give **6a** and **b** is presumably facilitated by the OMgBr (Scheme 2). When the reaction was repeated with phenyllithium on **1** the alcohol **6**

was obtained in a very poor yield. Attempts to cyclise **6** to **4** by azeotropic distillation in *p*-xylene with traces of *p*-toluenesulphonic acid and also by refluxing with sodium methoxide failed as the reaction gave elimination product **9** rather than the displacement product **4**.

The Grignard reaction was repeated with the diacetate **2**[4] which is expected to be a good leaving group but surprisingly, 1,1-diphenylethanol (**10**), confirmed by mixed melting point determination with an authentic sample, was obtained. This showed that the phenyl group had attacked the ester group rather than the acetal group. A better leaving group was provided by the synthesis of 2,5-dibromo-2,5-dihydrofuran (**3**). The reaction of this compound could be regarded a analogous to that of the glycosyl halide (**11**) which reacts with phenylmagnesium bromide yielding the C-glycoside **12**[5,6]. Though the dibromide **3** was not isolated there was PMR spectra evidence[7] for the formation of the *cis*- and *trans*-isomers at low temperature.

Indeed when furan was oxidised with bromine in dry ether at $-78°$ and then treated with two equivalents of phenylmagnesium bromide for 4 hr, a mixture of products was obtained on work-up which was resolved by column chromatography to give two isomers of **4** in 58% yield. The PMR spectrum of **4** showed two singlets at δ 5.82 and 5.90 each of which integrated for two protons as has been observed in the spectra of the dimethoxy (**1**)-, diacetoxy (**2**)- and dibromo (**3**)-dihydrofurans. The appearance of H-2, H-5 and H-3, H-4 as singlets in both the products suggests that there was no coupling between them.

Experimental Procedure

Melting points were determined on a hot-stage microscope and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Pye-Unicam SP1050 spectrophotometer, PMR spectra (chemical shifts in δ-scale) in $CDCl_3$ on a Varian HA100 spectrometer using TMS as internal standard and mass spectra on an AET MS9 double focussing instrument at 25° and 70 eV. TLC was performed on silica gel GF 254 plates using the solvent systems: methylene chloride-ethyl acetate (10:1) (system F), methylene chloride (system L) and methylene chloride-pet. ether 40-60 (1:1) (system K). Nitrogen refers to oxygen free nitrogen dried by passing successively through conc. sulphuric acid and calcium chloride. All laboratory reagents were purified before use.

2,5-*Dihydro*-2,5-*dimethoxyfuran* (**1**)

For details of procedure see ref. 3. Yield 70% (34.7 g), b.p. 50-60° at 3 mm Hg; IR (film): 3050-2900, 1608; MS: m/z 98 (M^+-CH_3OH); PMR: 3.28, 3.32 (s, 6H, $2\times -OCH_3$), 5.54 (s, 2H, $-CH=CH-$), 5.81, 6.00 (s, 2H, $2\times -CHOCH_3$).

1,4-*Diphenyl*-4-*methoxy*-*but*-2-*en*-1-*ol* (**6**)

A solution of compound **1** (2.01 g, 15.5 mmol) in dry ether (25 ml) was added through the septum cap by a syringe into a two-necked flask prefilled with nitrogen. Phenylmagnesium bromide (26 ml, 49 mmol, 1.96 *M* in ether) was then added by syringe and the reaction mixture stirred at $-10°$ for 10 min, allowed to warm up to room temperature within 4 hr, acidified with aq. NH_4Cl (*p*H 4) and extracted with ether (30 ml × 3). The extract was washed with water (30 ml × 2), dried (Na_2SO_4) and evaporated to give an oil (3.2 g). TLC of this oil (system F) showed two spots with R_f 0.69 and 0.53. The mixture was separated on a column of silica gel using the same solvent system to give two isomers.

Isomer **6a** (oil): Yield 36% (1.4 g); IR (film): 3400, 3090-2840, 1605; MS: m/z 236 (M^+-H_2O); PMR: 3.10 (s, 3H, $-OCH_3$), 3.18 (br s; 1H, exchangeable with D_2O, $-OH$), 4.96 (dd, 1H, $-CHOCH_3$, J = 2,6), 5.47 (m, 1H-C*H*OH), 5.48-5.96 (m, 2H, $-CH=CH-$), 7.10-7.38 (m, 10H, arom. protons).

Isomer **6b**: Yield 15.4% (0.601 g), m.p. 73-75°; IR (KBr): 3350, 3095-2820, 1605; MS: m/z 236 (M^+-H_2O); PMR: 3.22 (s, 3H, $-OCH_3$); 3.32 (br s; 1H, exchangeable with D_2O, $-OH$), 5.04 (dd, 1H, $CHOCH_3$, J = 2,6), 5.40 (m, 1H, $-CHOH$), 5.64-5.76 (m, 2H, $-CH=CH-$), 7.20 (s, 10H, arom. protons).

1-*Acetoxy*-1,4-*diphenyl*-4-*methoxybut*-2-*ene* (**7**)

A solution of **6a** and **6b** (200 mg, 0.78 mmol) in dry pyridine (5 ml) and excess acetic anhydride (202 mg, 1.9 mmol) was stirred at room temperature overnight. The reaction mixture was poured into ice cold water, kept for 30 min and extracted with diethyl ether (25 ml × 3). The ether layer was washed with 1 *M* HCl (20 ml × 2), $NaHCO_3$ solution (20 ml × 2) and water (20 ml × 2). After drying (Na_2SO_4) and evaporation, an oil was obtained from each reaction.

Isomer **7a**: Yield 80.7% (188 mg) from **6a**; IR (film): 3080-2800, 1740, 1610; MS m/z 236 (M^+-CH_3COOH); PMR: 1.96 (s, 3H, $-OCOCH_3$), 3.17 (s, 3H, $-OCH_3$), 5.18 (dd, 1H, $-CHOCH_3$, J = 2,5), 5.64-5.78 (m, 2H, $-CH=CH-$), 6.78 (dd, 1H, $-CHOCOCH_3$, J = 2,5), 7.16-7.46 (m, 10H, arom. protons).

Isomer **7b**: Yield 77.3% (180 mg) from **6b**: IR (film): 3100-2860, 1745, 1610; MS: m/z 236 (M^+-CH_3COOH): PMR: 2.02 (s, 3H, $-OCOCH_3$), 3.30 (s, 3H, $-OCH_3$), 5.20 (dd, 1H, $CHOCH_3$, J = 2,5),

5.70-5.80 (m, 2H, $-CH=CH-$), 6.66 (dd, 1H, $-CHOCOCH_3$, J = 2,5), 7.22 (s, 10H, arom. protons).

2,5-*Dihydro*-2,5-*diphenylfuran* (**4**)

A solution of furan (2 g, 29.4 mmol) in dry diethyl ether (25 ml) was added by syringe into a three-necked flask fitted with a pressure equalising funnel. A cold (0°) solution of bromine (4.7 g, 29.4 mmol) in dry diethyl ether (25 ml) was added dropwise over a period of 30 min with vigorous stirring while keeping the temperature at −78°. A solution of phenylmagnesium bromide (38 ml, 59 mmol) in dry diethyl ether was then added by a syringe and the mixture allowed to warm up to room temperature within 4 hr. The reaction mixture was hydrolysed with aq. NH_4Cl, extracted with ether (30 ml × 3), washed with water (25 ml × 2) and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was separated on a column of silica using the solvent system K to give two isomers.

Isomer **4a** (oil): Yield 50% (3.3 g); IR: 3090-2860, 1605; MS: m/z 222 (M^+); PMR: 5.82 (s, 2H, 2 × $-OCHPh-$), 6.94 (s, 2H, $-CH=CH$); 7.24-7.36 (m, 10H, arom.).

Isomer **4b**: Yield 8% (0.52 g), m.p. 282-85°; IR (KBr): 3090-2980, 1610; MS: m/z 222 (M^+); PMR: 5.90 (s, 2H, 2 × $-OCHPh-$), 6.14 (s, 2H, $-CH=CH-$), 7.30 (m, 10H, arom. protons).

1,4-*Dimethoxy*-1,4-*diphenylbut*-2-*ene* (**8**)

A solution of **6b** (300 mg, 1.18 mmol) in dry methanol (15 ml) containing conc. HCl (3 drops) was refluxed for 1 hr. The mixture was cooled, diluted with water (30 ml) and extracted with chloroform (20 ml × 3). The chloroform extract was washed with water (25 ml × 2) and dried (Na_2SO_4). Evaporation of the oil gave an oil which showed two overlapping spots having R_f 0.72 on TLC (system F), yield 92% (291 mg); IR (film): 3080-2890, 1605; MS: m/z 236 (M^+-CH_3OH); PMR (isomer **8a**): 3.20 (s, 6H, 2 × $-OCH_3$), 3.80 (dd, 2H, C-1 and C-4, protons J = 2,6 Hz), 6.20 (m, 2H, $-CH=CH-$, 7.05 (m, 10H, arom.); PMR (isomer **8b**): 3.30 (s, 6H, 2 × $-OCH_3$), 4.24 (dd, 2H, C-1 and C-4 protons, J = 2,6 Hz), 6.34 (m, 2H, $-CH=CH-$), 7.36 (m, 10H, arom.).

1,4-*Diphenylbut*-3-*en*-1-*one* (**9**)

A solution of **6b** (225 mg, 0.89 mmol) in dry *p*-xylene (40 ml) containing traces of *p*-toluenesulphonic acid was refluxed overnight with CaH_2 in a Soxhlet extractor. The solvent was evaporated and the oil obtained was dissolved in ether (4 ml) and passed down a short column of silica gel. Evaporation of ether gave a clear oil which solidified on standing, yield 95% (187 mg), m.p. 68-70°; IR (KBr): 3100-2860, 1680, 1610, MS: m/z 222 (M^+); PMR: 3.75 (m, 2H, C-2 proton); 5.52-5.74 (m, 1H, C-3 proton), 6.58 (d, 1H, C-4 proton, J = 4), 6.90-7.40 (m, 10H, arom. protons).

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Synthesis of imidazo-, pyrazino- and diazepino-quinoxalines from quinoxaline-5, 6-diamine and ketones

S Krishan Rao, A Pandu Ranga Reddy & V Veeranagaiah*
Department of Chemistry, Osmania University, Hyderabad 500 007

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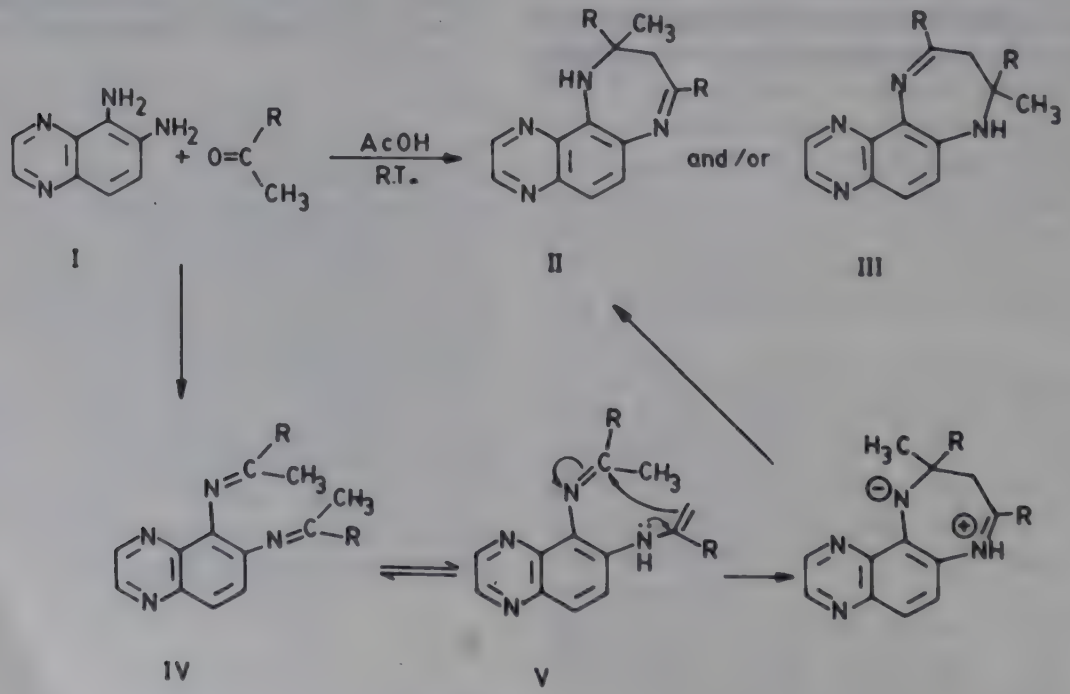
Condensation of quinoxaline-5, 6-diamine (I) with acylic ketones in acetic acid followed by pyrolysis gives 2, 4, 5-trialkyl-2, 3-dihydro-1*H*-[1,4]diazepino[2, 3-*f*]quinoxalines (II), 1,2-dihydro-3-phenylpyrazino[2,3-*f*]quinoxalines (VI) and 3*H*-imidazo[4, 5-*f*]quinoxalines (VII-IX). However, with cyclic ketones the diamine I yields 3′,4′-cycloalkanospiro[cycloalkane-1, 2′-[1*H*]-[1,4]diazepino[2,3-*f*]quinoxaline derivatives (X-XIII)

In our preceding papers[1,2], the formation of 1*H*-imidazo[4,5-*f*]quinoxalines was reported by the reaction of quinoxaline-5,6-diamine (I) with aldehydes and acids. We now report the results of the reactions of I with various ketones.

The diamine (I) on reaction with butan-2-one in 1 : 2 molar proportion in acetic acid yielded a compound which on the basis of spectral and analytical data was characterized as 2,4-diethyl-2-methyl-2, 3-dihydro-1*H*-[1,4]diazepino[2, 3-*f*]quinoxaline (IIb). The reaction of I was extended to three other ketones, propan-2-one, pentan-2-one and 3-methylbutan-2-one, and in each case the corresponding 2, 4, 4-trialkyl-2, 3-dihydro-1*H*-[1,4]diazepino[2, 3-*f*]quinoxaline (IIa, IIc and IId) (Scheme 1) was obtained in moderate yields (Table 1).

The formation of II, instead of the isomeric 2, 4, 4-trialkyl-5*H*-[1,4]diazepino[2, 3-*f*]quinoxaline (III) can be explained as follows. Of the two tautomeric forms possible for dianil (IV) obtained by the 1 : 2 reaction of I with ketone, V may preferentially be formed from IV since 6-amino group is more basic than 5-amino group[3,4]. The tautomer V undergoes cyclisation via the transition state (**A**) which is energetically moe feasible due to maximum dispersal of negative charge on C-5 nitrogen of quinoxaline (Scheme 1). This finds support from our earlier report in which 2, 4, 4-trialkyl-1*H*-[1,4]diazepine derivatives were the exclusive products from the



Scheme 1

Table 1—Physical data of diazepino-, pyrazino- and imidazo-quinoxalines

Compd	R	m.p. C	Yield (%)	Mol. formula*
IIa	CH_3	85	15	$C_{14}H_{16}$
IIb	C_2H_5	114	10	$C_{16}H_{20}N_4$
IIc	nC_3H_7	146	12	$C_{18}H_{24}N_4$
IId	i-C_3H_7	160	10	$C_{18}H_{24}N_4$
IIe	C_6H_5	124	15	$C_{24}H_{20}N_4$
IIf	C_6H_5	74	75	$C_{26}H_{24}N_4$
IIg	C_6H_5	253	17	$C_{28}H_{28}N_4$
VIa	H	183	25	$C_{16}H_{12}N_4$
VIb	CH_3	133	15	$C_{18}H_{16}N_4$
VII	C_6H_5	217	20	$C_{15}H_{10}N_4$
VIII	$C_6H_5CH_2$	190	57	$C_{16}H_{12}N_4$
IX	—	165	20	$C_{21}H_{14}N_4$
Xa (n = 4)	—	170	25	$C_{18}H_{20}N_4O_2$
Xb (n = 5)	—	200	38	$C_{20}H_{24}N_4O_2$
XIa (n = 4)	—	200	20	$C_{18}H_{20}N_4$
XIb (n = 5)	—	205	18	$C_{20}H_{22}N_4O$
XII	—	72	12	$C_{22}H_{28}N_4$
XIIIa (n = 4)	—	80	10	$C_8H_{20}NCl$
XIIIb (n = 5)	—	62	15	$C_{20}H_{24}N_4$

*All the compounds gave satisfactory C, H and N analyses.

reaction of quinoline-5, 6-diamine with methyl ketones[5].

However, the reaction of I with acetophenone in acetic acid at room temperature yielded a new product (m.p. 183°C), characterised as 3-phenyl-1, 2-dihydro[1, 4]pyrazino[2, 3-*f*]-quinoxaline (VIa) in addition to 2,4-diphenyl-2-methyl-1*H*-[1,4]diazepino[2, 3-*f*]quinoxaline (IIe). This reaction when carried out under thermal conditions in the absence of any solvent yielded IIe and 2-phenyl-1*H*-imidazo[4,5-*f*]quinoxaline[1] (VII). The reaction of I with phenyl ethyl and phenyl isopropyl ketones did not proceed at room temperature. However, under thermal conditions phenyl ethyl ketone yielded IIf and VII and with phenyl isopropyl ketone IIg and VIb (Scheme 2).

The formation of VIa and VII in addition to IIe from the reaction of I and acetophenone under different experimental conditions may be explained as follows. The diamine I reacts with acetophenone in equimolar ratio to give a monoanil (**B**) which may either tautomerise and then undergo dehydrogenative cyclisation to give VIa or may simply undergo cyclisation by elimination of the elements of methane through zoline form to give VII. However, the compound II in these reactions may result from the dianil IV which may be formed from the reaction of monoanil (**B**) with another molecule of acetophenone (Scheme 2).

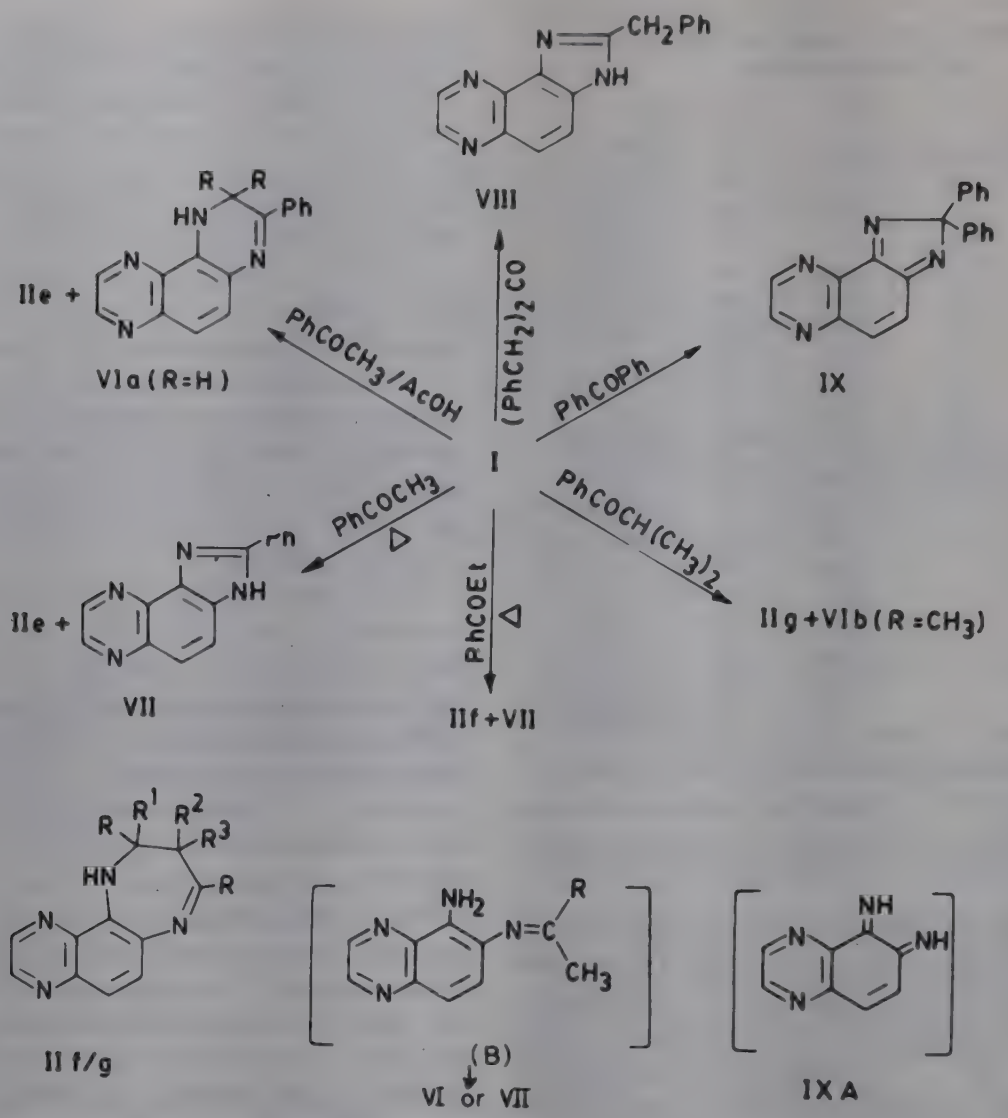
Dibenzyl ketone on reaction with I either in acetic acid or in the absence of any solvent at 200° for 2 hr resulted in a crystalline compound, identical (m.p., m.m.p., superimposable IR) with 2-benzyl-3*H*-imidazo[4,5-*f*]quinoxaline[2] (VIII; Scheme 2).

The reaction of I with benzophenone in acetic acid either at room temperature or on heating at 80-90° did not proceed. But, when an intimate mixture of I and benzophenone was heated at ~ 150° in the absence of any solvent, yielded a product having m.p. 165°. Baded on spectral data this compound was assigned the structure 2,2-diphenyl-2*H*-imidazo[4,5-*f*]quinoxaline (IX, Scheme 2).

The formation of IX as the sole product under thermal conditions probably takes place by the condensation of the diimine IXA, produced under reaction conditions, with benzophenone. This finds support from the reaction of quinoline-5, 6-diamine with benzophenone[5].

Cyclopentanone on reaction with I at room temperature in acetic acid yielded two crystalline products with m.ps 170° and 200°. Based on spectral data and elemental analysis the compound with m.p. 170° was characterised as 3′-hydroxy-3′,4′-cyclopentanospiro[cyclopentane-1, 2′(3′*H*)-[1*H*]-[1,4]diazepino-[2, 3-*f*]quinoxaline]-5′-oxide (Xa) and the other compound with m.p. 200° as 3′,4′-cyclopentenospiro[cyclopentane-1, 2′(3′, 4′-cyclo pentenosprio[cyclopentane-1, 2′(1′*H*)-[1,4]diazepino[2,3-f]quinoxaline]-5′-oxide (XIa) (Scheme 3). On extending the reaction of I with cyclohexanone the two compounds obtained were characterised as the corresponding products Xb and XIb. However, the reaction of I with cycloheptanone in acetic acid resulted in a single crystalline product, characterised as 3′,4′-cycloheptanospiro-[cycloheptane-1, 2′(3′*H*)-[1*H*][1,4]diazepino[2,3-*f*]quinoxaline] (XII) as revealed by its spectral data. Attempts to obtain the corresponding X and/or XI, either from XII or directly from the reaction of I and cycloheptanone were unsuccessful.

Attempts under different experimental conditions were made to study the stability and reactivity of X and XI. Compound X on treatment with PCl_3/$CHCl_3$ yielded a crystalline product, identical with XI. Compound XI could also be obtained by heating X in diphenyl ether under reflux for 2 hr. This process involved the simple elimination of elements of water. But, the compound X or XI when independently treated with iron in acetic acid, gave in a single crystalline product, characterised as the corresponding 3′,4′-cycloalkanospiro[cycloalkane-1,2′-(3′*H*)-[1*H*]-[1,4]diazepino[2,3-*f*]quinaxaline]--5′-oxide (XIII) (Scheme 3). The OH group at C-3′ of X and the double bond at C-3′ of XI were reduced by iron and acetic acid in this process. However, in both the compounds (X and XI) the 5′-oxide remained intact and was not effected by the reaction



Scheme-2

conditions. These conversions were supported by the report on the reactions of benzene-1,2-diamine with cyclopentanone[6].

Experimental procedure

Condensation of quinoxaline-5, 6-diamine (II) with methyl alkyl ketones: General procedure

Appropriate ketone (0.02 mol) was added to a solution of I (0.01 mol) in minimum amount of gl. acetic acid (10 ml) while shaking. The reaction mixture was allowed to stand at room temperature for 4 hr and then poured in 100 ml of ice water and neutralised with ammonia. The resinous mass that separated was extracted with chloroform, concentrated and subjected to column chromatography over neutral alumina using an appropriate solvent as eluant to give the corresponding 2,4,4-trialkyl-2, 3-dihydro-1*H*-[1,4]diazepino[2,3-*f*]quinoxaline (IIa-d; Table 1). The spectral data of representative compounds are given below:

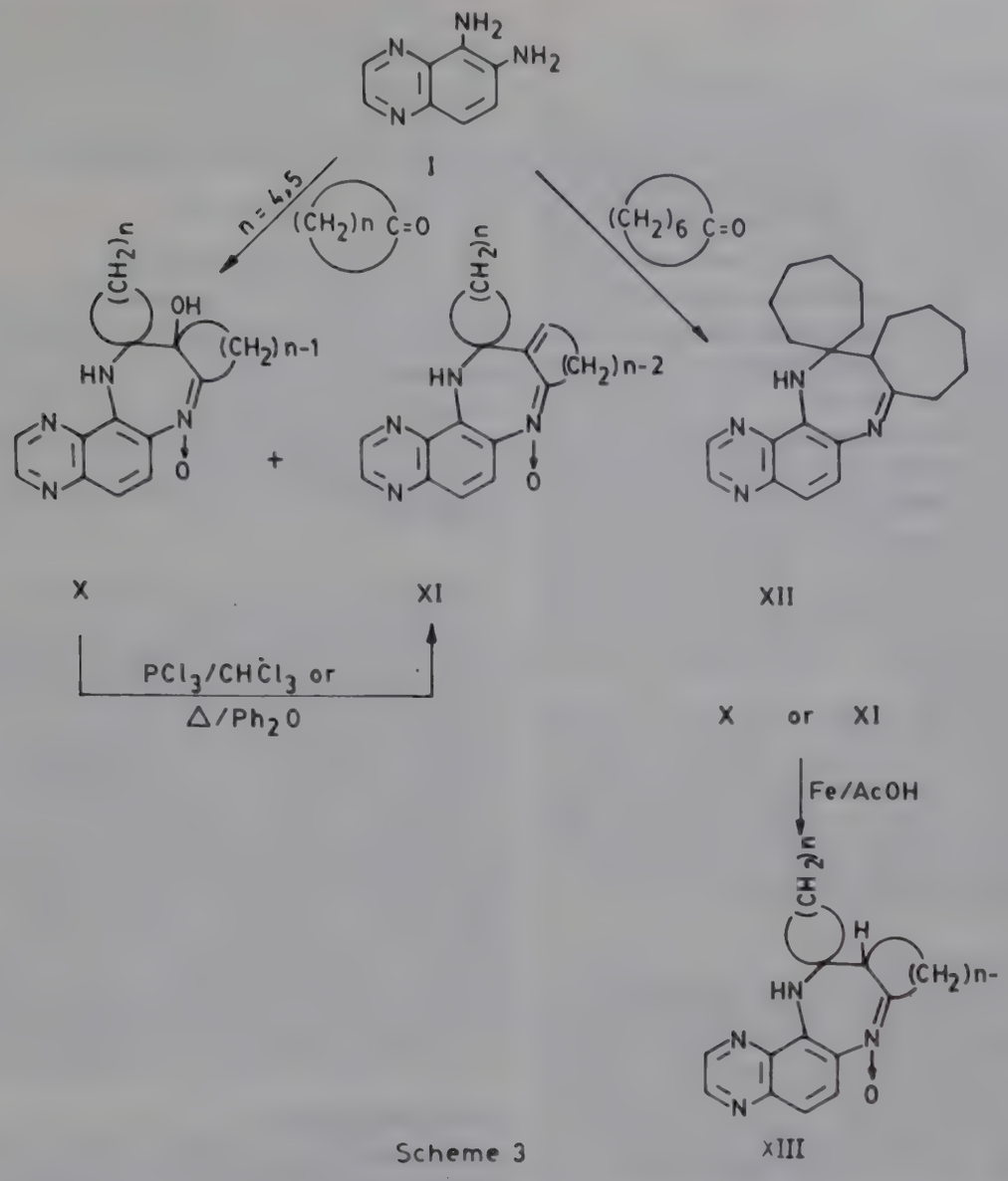
IIa—IR (KBr): 3300 cm^{-1} (NH); PMR ($CDCl_3$): δ 1.45 (s, 6H, $2CH_3$), 2.4 (s, 3H, $N=C-CH_3$), 2.5 (s, 2H, $-CH_2-$), 6.5 (br, 1H, NH, D_2O exchangeable), 7.52 (dd, 2H, aromatic protons), 8.68 (dd, 2H, $-N=CH-CH=N-$ of quinoxaline moiety); MS: m/z 240 ($M^{+\cdot}$).

IIg—IR (KBr): 3300 (NH), 1665 cm^{-1} (C=N); PMR ($CDCl_3$): δ 1.47 (d, 6H, $2\times CH_3$), 1.49 (s, 6H, $2\times CH_3$), 3.38 (br, 2H, D_2O exchangeable, NH and $>CH-$), 7.5 (m, 10H, aromatic), 8.00 (dd, 2H, aromatic protons), 8.83 (dd, 2H, $N=CH-CH=N$ of quinoxaline ring).

Condensation of I with phenyl alkyl ketones

(a) In acetic acid

The reaction of I (0.01 mol) with appropriate ketone (0.02 mol) was carried and the reaction mixture



Scheme 3

worked up as above. Elution of the column with benzene and benzene-ethyl acetate (9 : 1) gave II and VI respectively.

VIa—IR (KBr): 3250 (NH), 1575 cm^{-1} (C=N); PMR ($CDCl_3$): δ 3.0 (d, 3H, NH and CH_2), 6.5-7.75 (m, 7H, aromatic protons), 8.4 (m, 2H, N=CH=CH=N of quinoxaline ring); MS: m/z 258 ($M^{+\cdot}$-2).

(b) Under thermal conditions

A mixture of I (1.2 g) and excess of an appropriate ketone (10 ml) was heated under reflux for 3 hr. The gummy material obtained after removal of the excess ketone was passed through a column of neutral alumina to yield two crystalline compounds in each case, the corresponding II and VII from benzene and benzene-ethylacetate (8 : 2) fractions, respectively.

Condensation of I with dibenzyl ketone

The diamine I (0.05 mol) was dissolved in acetic acid (10 mol) and dibenzyl ketone (0.05 mol) added to the solution dropwise while shaking. The reaction mixture was worked up as above and the product chromatographed using benzene-ethyl acetate (9 :1) as eluant to give 2-benzyl-1*H*-imidazo[4,5-*f*]quinoxaline (VIII); IR (KBr): 3600-2500 cm^{-1} (NH); PMR (TFA): δ 4.7 (s, 2H, CH_2Ph), 7.3 (m, 5H, aromatic protons), 8.4 (dd, 2H, aromatic protons), 8.7 (dd, 2H, −N−CH−CH=N− of quinoxaline ring); MS :m/z 260 ($M^{+\cdot}$).

Condensation of I with benzophenone

An intimate mixture of I (0.01 mol, 1.6 g) and benzophenone (0.01 mol, 1.82 g) in a test tube was heated at 200-20° on a wurtz metal bath for 5 hr. The resulting black mass was passed through a column of neutral alumina using benzene as eluant to get 2,2-diphenyl-2*H*-imidazo[4,5-*f*]quinoxaline (IX); PMR ($CDCl_3$): δ 7.2-7.6 (m, 10H, aromatic protons), 7.95-8.25 (dd, 2H, aromatic protons), 8.6 (dd, 2H, −N=CH−CH=N− of quinoxaline ring); MS: m/z 322 ($M^{+\cdot}$).

Condensation of I with cyclic ketones

(*a*) *With cyclopentanone and cyclohexanone*

To a solution of I (0.01 mol) in acetic acid (10 ml) an appropriate cyclic ketone (0.02 mol) was added dropwise with thorough shaking. The reaction mixture was kept aside for overnight. The resulting dark solution was diluted with cold water and neutralised with ammonia to yield a resinous material. It was subjected to chromatography over a column of neutral alumina using pet. ether-benzene (1 : 1) and benzene as eluants to obtain, in each case, the corresponding X and XI respectively (Table 1).

Xa—IR (KBr): 3480-3300 (OH), 3250 (NH), 1575 cm^{-1} (C=N); PMR ($CDCl_3$): δ 1.4-2.87 (m, 15H, $7\times CH_2$ and 1NH, D_2O exchangeable), 6.06 (1H, OH, D_2O exchangeable), 7.30 (d, 1H, aromatic protons), 8.17 (d, 1H, aromatic protons), 8.65 (dd, 2H, $-N=CH-CH=N-$ of quinoxaline ring); MS: m/z 324 ($M^{+\cdot}$).

XIa—IR (KBr): 3280 (NH), 1675 cm^{-1} (C=N); PMR ($CDCl_3$): δ 1.95 (m, 8H, $4\times CH_2$), 2.55 (m, 4H, $CH_2-C=N$, $CH_2-C=C$), 6.25 (b, NH, D_2O exchangeable), 6.6 (1H, C=CH), 7.35 (m, 2H, aromtic protons), 8.65 (dd, 2H, N=CH−CH=N of quinoxaline ring); MS: m/z 306 ($M^{+\cdot}$).

(*b*) *With cycloheptanone*

A mixture of I (0.01 mol) and cycloheptanone (0.02 mol) in acetic acid (10 ml) was kept at room temperature for 3 hr and the reaction mixture worked up as in the previous case using benzene-ethylacetate (9 :1) as eluant to give XII; IR (KBr): 3350 (NH), 1650 cm^{-1} (C=N); PMR ($CDCl_3$): δ 1.2-2.5 (b, 2OH, $10\times CH_2$), 2.75 (br, 3H, $CH_2-C=N$, $CH-C=N$), 6.85 (b, NH, D_2O exchangeable), 7.56 (d, 2H, aromatic protons), 8.70 (dd, 2H, N=CH−CH=N of quinoxaline ring); MS: m/z 348 ($M^{+\cdot}$).

Conversion of X to XI

(*a*) *Treatment with PCl_3 in $CHCl_3$*

To a chloroform solution of X (0.5 g), PCl_3 (1.6 ml) was added dropwise while cooling. The solution was allowed to stand at room temperature for 10 min and heated on a steam-bath for 30 min, diluted with 10 ml water and neutralised with NaOH (10%). The solution was extracted with $CHCl_3$, concentrated and chromatographed over a column of neutral alumina using pet. ether-benzene (1 : 1) as eluant to give XI.

(*b*) *Under thermal conditions*

Compound X (0.5 g) was dissolved in diphenyl ether (10 ml) and heated under reflux for 2 hr. The dephenyl ether was removed by steam distillation and the residue extracted with chloroform. The solution was concentrated, chromatographed over a column of neutral alumina using benzene as eluant to give XI.

Treatment of X or XI with iron and acetic acid

Compound X or XI (0.5 g) was dissolved in acetic acid (15 ml) and iron powder (1 g) added to it. The reaction mixture was heated at 100° for 4 hr, cooled to room temperature and filtered. The filtrate, after dilution with water, was neutralised with NaOH (10%) and extracted with chloroform. The concentrate of $CHCl_3$ extract was adsorbed over a column of neutral alumina and eluted with benzene to give XIII; IR (KBr): 3350 cm^{-1} (NH); PMR ($CDCl_3$): δ 1-2.75 (b, 19H, $9\times CH_2$, CH), 6 (br, NH, D_2O exchangeable), 7.2 (d, 1H, aromatic protons), 7.4 (d, 1H, aromatic protons), 8.6 (dd, 2H, $-N=CH-CH=N-$ of quinoxaline ring).

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[4n + 2]π-Cycloadditions of 1-(6-arylpyridazin-3-yl)-3-oxidopyridinium betaines with 2π-1,3-dipolarophiles

S A El-Abbady†, H A Abdel-Hamid*, A A Shalaby, M G Ahmed† & A H Moustafa
Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo, A R Egypt

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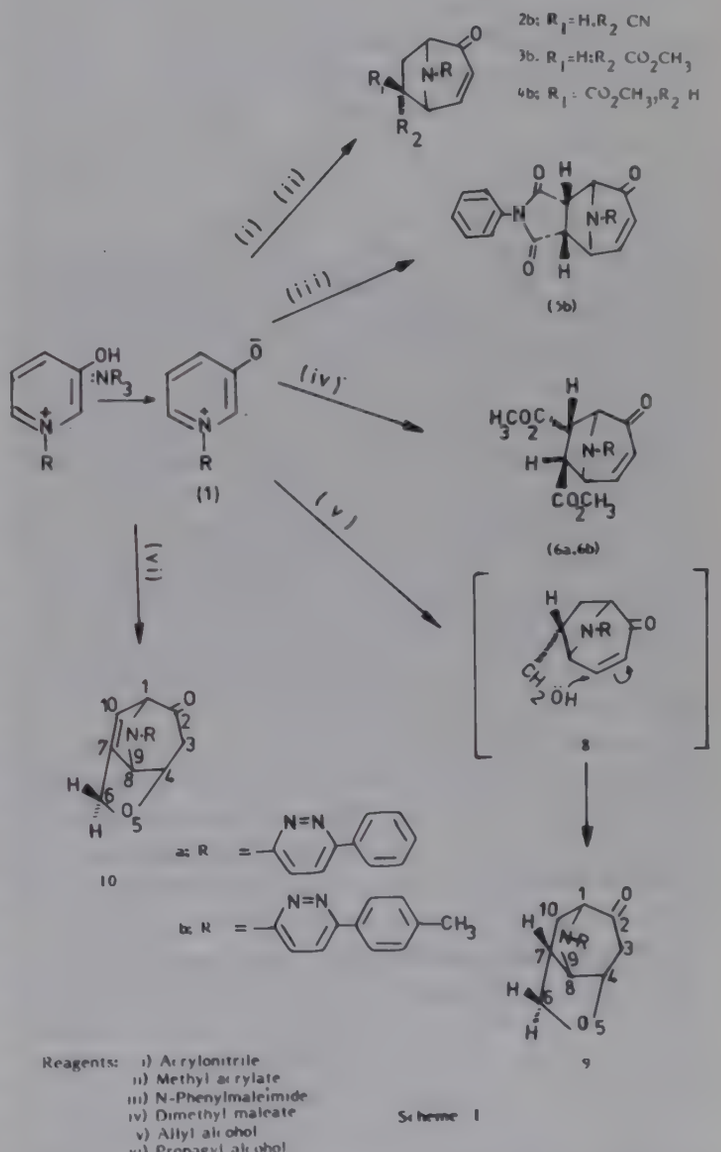
1-(6-Phenylpyridazin-3-yl)- and 1-[6-(*p*-tolyl)pyridazin-3-yl]-3-oxidopyridinium betaines (**1a,b**) react as 1,3-dipoles across 2- and 6-positions with olefinic and acetylinic 2π-1,3-dipolarophiles, to give the cycloadducts (**2b,3b,5b,6a,b,7a,9b,10a**), the stereochemistry of which has been deduced from PMR spectra.

The 1-(3-pyridazinyl)-3-oxidopyridinium betaines with two adjacent annular nitrogen atoms in 2- and 3-positions[1,2] show reactivity comparable with that of the highly reactive betaines[3] such as 1-(4-pyridyl), and 1-(*s*-triazinyl) possessing annular nitrogen atoms in 2,4 and 6-positions. The enhanced reactivity of 1-(6-arylpyridazin-3-yl)-3-oxidopyridinium betaines (**1a,b**) has been currently investigated by MO calculations and kinetics studies and the results will be published in due course. In this paper we report the results of our study on the thermally allowed [4πs + 2πs]-1,3-dipolar cycloadditions of the betaines **1a** and **1b** with a variety of 2π-electron deficient 1,3-dipolarophiles.

The required betaines (**1a,b**) were not isolated. Their dimeric forms were photosensitive and readily decomposed after isolation. Consequently addition reactions were conducted on the *in situ* generated unstable betaines (**1**) from the corresponding quaternary salts, in presence of the dipolarophile. Thus, betaine **1b** reacted with acrylonitrile to give the *endo*-6-cyano-8-azabicyclo[3.2.1]oct-3-en-2-one (**2b**) (Scheme 1) and no product corresponding to the *exo*-isomer could be isolated. Configurational assignment of **2b** was provided by its IR and PMR spectra. In particular the appearance of H-5 signal as a triplet at δ 5.64 could be attributed to its coupling with H-4 and *exo*-H-6. This is compatible with the *endo*-configuration of the cyano group at C-6. The IR absorption at 1680 confirmed the presence of the conjugated carbonyl group and the absorption at 2230 cm^{-1} was attributed to the cyano group. The electronic spectrum of **2b** exhibited a λ_{max} at 275 nm due to n-π* transition. The isolation of the 6-*endo*-stereoisomer as a single cycloadduct parallels to that recorded for the corresponding cycloaddition with 1-(6-phenylpyridazin-3-yl) betaine (**1a**)[4] and 1-(4-pyridyl) betaine[5] which is in accord with the MO calculations[6], but it is contrary to the cycloaddition of 1-phenyl[7], 1-(2-pyridyl)[4] and 1-(*s*-triazinyl)[8] betaines. The latter yielded both the *endo*-



Scheme 1

†Department of Chemistry, University College for Women, Ain Shams University, Heliopolis, Cairo, A R Egypt.

and *exo*-stereoisomers in almost equal amounts. However, in the case of methyl acrylate the regioselectivity and stereoselectivity were maintained. Thus, the betaine **1b** gave the kinetically controlled *endo*-cycloadduct 6-*endo*-methoxycarbonyl-8-[6-*p*-tolyl)-pyridazin-3-yl]-8-azabicyclo[3.2.1]oct-3-en-2-one (**3b**) as the major product, whereas the exoisomer **4b** (< 10%) could not be isolated but its presence was detected in the PMR spectrum. Configurational assignment was inferred from elemental analysis and spectral data. The IR spectrum exhibited characteristic absorptions at 1690 (conjugated ketonic C = O) and 1730 cm^{-1} (ester C = O). The PMR spectrum showed the *endo*- and *exo*-configurations for the methoxycarbonyl group at C-6, based on the splitting of H-5 as a triplet at δ 4.68 and as a doublet at 5.64, respectively.

Analogous treatment of **1b** with N-phenylmaleimide afforded the kinetically controlled product 2-oxo-8-[6-(*p*-tolyl)pyridazin-3-yl]-8-azabicyclo[3.2.1] oct-3-ene-6,7-*endo*-dicarboxylic—N-phenylimide (**5b**) as a single stereoisomer in a fairly good yield. Its structural and configurational assignments were deduced from the elemental analysis and spectral data. The IR spectrum exhibited a band at 1680 characteristic of a conjugated carbonyl function and a broad band at 1730-1760 cm^{-1} assignable to the imide carbonyls. The PMR spectrum showed the H-5 as a doublet of doublets at δ 5.8 indicative of the *endo*-stereoisomer. It should be noted that *exo*-isomer has been reported[7] to be isolated in some cases where N-phenylmaleimide was used. This was attributed to the isomerisation of the initially formed kinetically controlled *endo*-isomer to the more stable thermodynamically controlled *exo*-isomer under prolonged heating of the reaction mixture (4-5 days). However, such epimerisation may not take place in our case due to the relatively shorter reaction period (12 hr).

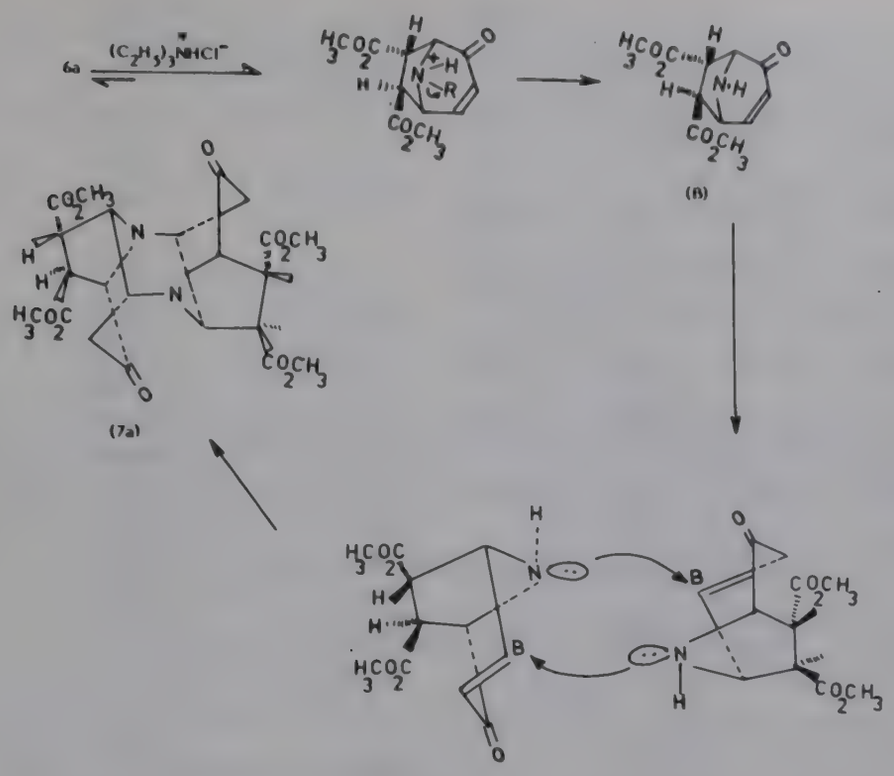
Betaines **1a** and **1b** reacted as 4π-components with dimethyl maleate to give unexpectedly the fumarate cycloadducts (**6a,6b**) as the single stereoisomers in moderate yields. The IR spectra of the cycloadducts (**6a** and **6b**) exhibited the stretching frequencies of the three carbonyl groups at 1680 (C = O, conjugated), 1720 and 1730 (two differently oriented ester carbonyls). The PMR spectra of the cycloadducts **6** confirmed the products to be fumarate adducts rather than the maleate isomers. The H-1 appeared as a doublet at δ 5.06 due to its coupling with *exo*-H-7 ($J_{1,7\text{-}exo}$ = 9 Hz, $J_{1,3} \simeq 1$ Hz) supporting the *exo*-configuration of H-7. On the other hand H-5 appeared as a doublet at δ 5.70 ($J_{4,5}$ = 5 Hz, $J_{5,6\text{-}endo}$ = 1 Hz) which established the *endo*-configuration of H-6. Moreover, methyl protons of the methoxycarbonyl groups produced two adjacent singlets at δ 3.72 and 3.74 in favour of the fumarate cycloadduct.

The isolation of fumarate cycloadduct as the sole product and no maleate isomer being detected even by PMR spectra of the products (**6a** and **6b**) indicates that the reaction is apparently non-stereospecific which is contrary to the most acceptable concerted mechanism proposed by Huisgen[11] and later by Katritzky[1] for 1,3-dipolar cycloadditions. Two possible pathways are possible for the formation of **6**. (i) Isomerisation of dimethyl maleate prior to addition under the condition of the reaction or (ii) isomerisation of the initially formed kinetically controlled maleate cycloadduct to the thermodynamically stable fumarate isomer due to steric considerations.

Dimethyl maleate is known to isomerise partially to the fumarate isomer on heating in the presence of triethylamine. However, owing to the isolation of the fumarate cycloadduct as the sole product, the first pathway has been excluded. So, the apparent nonstereospecificity of the cycloaddition may be rationalised via an initial addition of the dimethyl maleate to the betaines (**1a** and **1b**) to give the kinetically controlled maleate cycloadducts which are transformed to the thermodynamically stable fumarate cycloadducts (**6a** and **6b**) through epimerisation either at C-6 or C-7 depending upon whether the maleate adducts have the *endo*- or *exo*-configuration. We are inclined that the initially formed maleate adduct has the *endo*-configuration of the two ester groups in which the steric interaction may promote the possible epimerisation at C-6. This would be in agreement with the concertedness of the cycloaddition process.

From the reaction of dimethyl maleate with **1a**, a colourless solid (**7a**) was also isolated in less than 10% yield. Its IR spectrum showed strong carbonyl absorptions at 1710 and 1720 cm^{-1} assignable to two types of non-conjugated carbonyl groups. The product was found to be transparent in the UV region. This by-product could be assigned the structure **7a** based on a similar observation that has been published earlier[2]. Thus, it is believed that the 6-phenylpyridazin-3-yl moiety was expelled from **6a** via an acid hydrolysis induced by triethylamine hydrochloride liberated during the reaction to give the unstable non-isolable compound **B**. The latter underwent dimerisation involving a Michael-type addition of the bridge N-8 of one molecule to the C-4 of the other, to give the pyrazine **7a** (Scheme 2).

Allyl alcohol, another example of electron deficient 2π-1,3-dipolarophile, reacted in a similar manner with **1b** to give the tricyclic adduct 9-[6-(*p*-tolyl) pyridazin-3-yl] - *endo* - 5 - oxa - 9 - azatricyclo - [5.2.1.$0^{4,8}$]decan-2-one (**9b**). The formation of **9b** could be explained by an internal Michael addition of the initially formed kinetically controlled 6-*endo*-hydroxymethylcycloadduct (**8b**). The IR spectrum of



9b exhibited only a carbonyl absorption of saturated cyclic ketones at 1730 cm^{-1}.

Propargyl alcohol, as a 2π-acetylinic 1,3-dipolarophile, reacted with betaine **1a** to give the cyclic ether 9-(6-phenylpyridazin-3-yl)-*endo*-5-oxa-9-azatricyclo[5.2.1.$0^{4,8}$]dec-6-en-2-one (**10a**) as evident from elemental analysis and spectral data. The IR spectrum of **10a** exhibited an absorption band near 1725 cm^{-1} for non-conjugated carbonyl group. The proposed structure was substantiated by its PMR spectrum.

Experimental Procedure

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer model 398 infrared spectrophotometer (ν_{max} in cm^{-1}), UV spectra in ethanol on a Specord (UV-Vis) Carlzeiss ultraviolet spectrophotometer (λ_{max} in nm and ε_{max} in parentheses), and PMR spectra in $CDCl_3$ on a Varian EM-390 spectrometer using TMS as internal reference (chemical shifts in δ, ppm). Chromatography was performed on alumina H-neutral. Characterization data of all the compounds prepared are given in Table 1.

6-endo-Cyano-8-[6-(p-tolyl)pyridazin-3-yl]-8-azabicyclo[3.2.1]oct-3-en-2-one (**2b**)

To a stirred solution of the salt **1b** (0.5 g, 0.0017 mol) and quinol (0.02 g) in acrylonitrile (20 ml) was added triethylamine (1 ml) dropwise, and the whole mixture heated under reflux for 48 hr. The excess acrylonitrile was then evaporated under reduced pressure to give a viscous material which was rendered free from triethylamine hydrochloride and the unreacted betaine by trituration with distilled water. The residue was boiled with ether under reflux for 30 min. The solid left was chromatographed over alumina (H-neutral) using ethyl acetate-light petroleum (3:1) as eluant to give a yellow solid which was crystallized from a proper solvent to give **2b**; IR; 2230 (C≡N), 1680 (C=O); UV: 275 (6.2×10^3); PMR: 4.66 (d, 1H, H-1), 6.06 (dd, 1H, H-3), 6.96 (q, 1H, H-4), 5.64 (t, 1H, H-5), 3.55 (sextet, 1H,H-6-*exo*), 2.94 (octet,1H,H-7-*exo*), 2.28 (q,1H,H-7-*endo*), 3.36 (s, 3H, CH_3), 7.86 (d, 1H,H-4′), 7.68 (d, 1H, H-5′), 7.49 (d, 2H, H-2″ and H-6″) and 7.38 (d, 2H, H-3″ and H-5″) ($J_{1,3}$ = 2.0 Hz, $J_{1,7\text{-}exo}$ = 8.0 Hz, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 6.0 Hz, $J_{5,6\text{-}exo}$ = 6.0 Hz, $J_{6,7\text{-}exo}$ = 10.0, $J_{6,7\text{-}endo}$ = 8.0 Hz and $J_{7\text{-}exo,7\text{-}endo}$ = 14.0 Hz).

Isomeric methyl 2-oxo-8-[6-(p-tolyl)pyridazin-3-yl]-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylates (**3b, 4b**)

To a stirred solution of **1b** (0.5 g, 0.0017 mol) and quinol (0.02 g) in methyl acrylate (20 ml), was added triethylamine dropwise, and the mixture heated under reflux for 48 hr, and worked-up as described above. The yellow solid obtained gave two very close spots on TLC, and was proved to be a mixture of unequal proportions of *endo*- and *exo*-6-methoxycarbonyl stereoisomers (**3b** and **4b**) difficult to separate; IR: 1725 (C=O ester), 1680 (C=O) and 1610, 1550 (skeletal vibrations of aromatic and heteroaromatic rings); UV:

Table 1—Characterization data of various compounds prepared

Compd.	Yield (%)	m.p. °C	Crystallized from	Colour	Mol. formula	Found % (Calc.)		
						C	H	N
2b	45	158-59	EtOAc	Yellow	$C_{19}H_{16}N_4O$	—	—	17.7
						(—	—	17.7)
3b,4b	40	188-91	EtOAc	Yellow	$C_{20}H_{19}N_3O_3$	68.3	5.0	11.6
						(68.7	5.4	12.0)
5b	80	186-87	EtOH	Pink	$C_{26}H_{20}N_4O_3$	71.2	5.0	—
						(71.5	4.6	—)
6a	35	173-75	MeOH	Yellow	$C_{21}H_{19}N_3O_5$	63.9	5.10	—
						(64.1	4.8	—)
6b	40	205-7	MeOH	Yellow	$C_{22}H_{21}N_3O_5$	—	—	10.2
						(—	—	10.3)
9b	20	145-47	EtOAc	Pale Yellow	$C_{19}H_{19}N_3O_2$	70.7	5.5	12.9
						(71.0	5.9	13.1)
10a	55	150-51	EtOH	Deep Yellow	$C_{18}H_{15}N_3O_2$	—	—	14.4
						(—	—	13.8)

276 (1.2×10^4); PMR: 4.15 (d,1H,H-1), 5.94 (dd,1H,H-3), 6.94 (q,1H,H-4), 4.68 (t,1H,H-5-*endo*), 5.64 (t,1H,H-5-*exo*), 3.65 (sextet, 1H,H-6), 2.94 (octet, 1H,H-7-*endo*), 2.15 (q,1H,H-7-*exo*), 2.35 (s, 3H, CH_3), 3.62 (s, 3H, $-O-C-CH_3$), 3.70 (s, 3H, $O-C-CH_3$), 7.82 (d,1H,H-4'), 7.62 (d,1H,H-5'), and 7.28 (m, 4H,$C_6H_4 \cdot CH_3$-*p*) ($J_{1,3} = 2.0$ Hz, $J_{1,7\text{-}exo} = 8.0$ Hz, $J_{3,4} = 10.0$ Hz, $J_{4,5} = 6.0$ Hz, $J_{5,6\text{-}exo} = 6.0$ Hz and $J_{6,7\text{-}exo} = 10.0$ Hz, $J_{6,7\text{-}endo} = 8.0$ Hz and $J_{7\text{-}exo,7\text{-}endo} = 14.0$ Hz).

2-Oxo-8-[6-(p-tolyl)pyridazin-3-yl]-8-azabicyclo-[3.2.1]oct-3-ene-6,7-endo-dicarboxylic N-phenylimide (**5b**)

To a solution of **1b** (0.5 g, 0.0017 mol), quinol (0.02 g) and N-phenylmaleimide (2.6 g, 0.015 mol) in tetrahydrofuran-chlorobenzene (1:1) (40 ml), triethylamine (1 ml) was added dropwise. The mixture was heated under reflux while stirring for 12 hr and worked-up as usual to give **5b**; IR: 1760-1730 (imido carbonyls), 1680 (C = O, conjugated), and 1600-1500 (skeletal vibrations of aromatic rings); UV: 254 (3×10^3) and 308 (1×10^3); PMR: 4.00 (dd, 1H,H-1), 6.30 (dd, 1H, H-3), 7.14 (dd, 1H, H-4), 5.80 (dd, 1H, H-5), 3.26 (dd, 1H, H-6-*exo*), 3.70 (dd, 1H, H-7-*exo*), 7.50 (m, 9H, C_6H_5 and $C_6H_4 \cdot CH_3$-*p*), 7.85 (d, 1H, H-4'), 7.70 (d, 1H, H-5'), 2.36 (s, 3H, CH_3) ($J_{1,3} = 1.0$ Hz, $J_{1,7\text{-}exo} = 8.2$ Hz, $J_{3,4} = 10.0$ Hz, $J_{4,5} = 5.0$ Hz, $J_{5,6\text{-}exo} = 7.0$ Hz, $J_{6\text{-}exo,\,7\text{-}exo} = 9.0$ Hz).

Dimethyl 8-(6-phenylpyridazin-3-yl)-8-azabicyclo-[3.2.1]oct-3-en-6-exo-7-endo-dicarboxylate (**6a**)

A mixture of **1a** (0.5 g, 0.0015 mol), quinol (0.02 g) and dimethyl maleate (2.2 g, 0.015 mol) in tetrahydrofuran-chlorobenzene (1:1) (40 ml) was treated similarly with triethylamine (1 ml) and heated under reflux for 48 hr. Working up as described above gave **6a**; IR: 1730, 1720 (ester carbonyls) and 1680 (C = O, conjugated), UV: 273 (4.5×10^3). A pyrazine derivative (**7a**) was also isolated in less than 10% yield as colourless crystals, m.p. 100-101°; IR:(KBr) 1710 and 1700 (C = O, saturated cyclic ketones).

Dimethyl 8-[6-(p-tolyl)pyridazin-3-yl]-8-azabicyclo-[3.2.1]oct-3-en-6-exo-7-endo-dicarboxylate (**6b**)

The reaction of **1b** was carried out as described above to give **6b**; IR: 1750, 1735 (ester carbonyls) and 1685 (C = O, conjugated), UV: 275 (1.8×10^4); PMR: 5.06 (d, 1H, H-1), 5.98 (dd, 1H, H-3), 7.50 (q, 1H, H-4), 5.70 (d, 1H, H-5), 3.68 (d, 1H, H-6-*endo*), 4.36 (d, H, H-7-*exo*), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.28 (m, 4H, $C_6H_4 \cdot CH_3$-*p*), 7.88 (d, 1H, H-4'), 7.70 (d, 1H, H-5') and 2.42 (s, 3H, CH_3) ($J_{1,3} = 1.5$ Hz, $J_{1,7\text{-}exo} = 7.7$ Hz, $J_{3,4} = 9.8$ Hz, $J_{4,5} = 4.8$ Hz, $J_{5,6\text{-}endo} = 0.4$ Hz, $J_{6\text{-}endo,\,7\text{-}exo} = 4.5$ Hz).

9-[6-(p-Tolyl)pyridazin-3-yl]-endo-5-oxa-9-azatricyclo[5.2.1.0^{4,8}]decan-2-one (**9b**)

A mixture of **1b** (0.5 g, 0.0017 mol) and allyl alcohol (10 ml) was treated with triethylamine (1 ml) and heated under reflux for 48 hr. Working up as described earlier afforded the tricyclic adduct **9b**; IR: 1725 (C = O, non-conjugated) and 1610 (C = C ring stretching), UV: 270 (2.3×10^4); PMR: 4.46 (d,1H,H-1), 6.84 (dd, 1H, H-3), 4.66 (q,1H,H-4), 3.83 (q, 1H, H-6-*exo*), 3.63 (dd, 1H, H-6-*endo*), 2.86 (m, 1H, H-7-*exo*), 5.36 (t, 1H, H-8), 2.40 (m,1H,H-10-*exo*), 1.62 (q,1H,H-10-

endo), 3.74 (s,3H,CH_3), 7.84 (dd,1H,H-4′), 7.75 (dd, 1H, H-5′), 6.92 (dd,2H,H-2″ and H-6″) and 7.49 (d, 2H, H-3″ and H-5″), ($J_{1,3}$ = 2.0 Hz, $J_{1,10\text{-}exo}$ = 8.00 Hz, $J_{3,4}$ = 10.0 Hz, $J_{4,8}$ = 6.0 Hz, $J_{8,7\text{-}exo}$ = 6.0 Hz, $J_{7,10\text{-}exo}$ = 10 Hz, $J_{7,10\text{-}endo}$ = 8.0 Hz, $J_{10\text{-}endo,\ 10\text{-}exo}$ = 14.0 Hz, $J_{7,H\text{-}6\text{-}exo}$ = 10 Hz, $J_{7,H\text{-}6\text{-}endo}$ = 10 Hz, and $J_{H\text{-}6\text{-}exo,\ H\text{-}6\text{-}endo}$ = 10.0 Hz).

9-[6-*Phenylpyridazin*-3-*yl*]-*endo*-5-*oxa*-9-*azatricyclo*-[5.2.1.$0^{4,8}$]-*dec*-6-*en*-2-*one* (**10a**)

To a mixture of **1a** (0.5 g, 0.0015 mol), quinol (0.02 g) and propargyl alcohol in ethanol (20 ml), was added triethylamine (1 ml) dropwise and the mixture refluxed for 24 hr. It was worked-up as described earlier to give **10a**; IR: 1725 (C = O, nonconjugated) and 1610 (C = C ring); UV: 280 (2.1×10^3); PMR: 4.92 (d, 1H, H-1), 6.90 (dd, 2H, $J_{1,3}$ = 2.00 Hz, H-3), 5.21 (q, 1H, $J_{3,4}$ = 10.0 Hz, H-4), 3.72 (q, 1H, $J_{6\text{-}exo,\ 6\text{-}endo}$ = 12.0 Hz, H-6-*exo*), 3.50 (dd, 1H,H-6-*endo*), 5.62 (d, 1H, $J_{4,8}$ = 6.00 Hz, H-8), 6.65 (d, 1H, $J_{1,10\text{-}exo}$ = 8.0 Hz, H-10-*exo*) and 7.40 (m, 5H, C_6H_5).

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Structure of dhaincha galactomannan from the seeds of *Sesbania bispinosa*†

V P Kapoor, A K Sen‡ & M I H Farooqi*
Natural Polymer Chemistry, National Botanical Research Institute, Lucknow 226 001 (India)

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The galactomannan, $[\alpha]_D^{30}$ + 22.0, isolated from the seed endosperms of *Sesbania bispinosa* contains D-galatose (1 mole) and D-mannose (1.9 moles). Hydrolysis of completely methylated galactomannan yields 2,3,4,6-tetra-O-methyl-D-galactose, 2,3,6-tri-O-methyl-D-mannose and 2,3-di-O-methyl-D-mannose in the molar ratio of 1.0 : 0.8 : 1.0. During periodate oxidation, it consumes 1.35 moles of periodate with the concomitant liberation of 0.37 mole of formic acid. Hydrolysis of the reduced oxo-polysaccharide gives only glycerol and erythritol in a molar ratio of 1 : 1.85. The weight average molecular weight (Mw) of the galactomannan has been found to be 2.29×10^5. The results of ^{13}C-NMR are in close agreement with the chemical shift assignment of the previously reported galactomannans. X-ray diffraction of the galactomannan has shown the same type of X-ray pattern as that of guar. On the basis of the above studies, it is established that the galactomannan is a branched polysaccharide consisting of the main chain of D-mannose units linked through β-(1 → 4) out of which about 50% of mannose units are attached to single D-galactose units through α-(1 → 6) linkages.

Sesbania bispinosa (Jacq) W.F. White (Syn. *S. aculeata* Pers.) commonly known in India as Dhaincha, is an annual leguminous plant belonging to the subfamily Papilionoideae. It is generally used for green manuring purposes and can be grown easily in alkaline and water-logged lands without much care and investment. Practically all parts of the plant are of economic utility. For instance, its stems are used for paper pulp and its seeds as cattle feed. The seeds are also supposed to be medicinally important and useful as laxative. The seeds of Dhaincha have been re ported to be possible source of a commercial gum[1–3]. It has been shown to be a galactomannan type of polysaccharide having useful sizing and stabilizing properties. It can be used in pharmaceutical preparations. In view of the growing importance of Dhaincha seed gum as a commercial product for export and use in various industries, structural studies of its galactomannan have been carried out and reported in the present paper.

As the galactomannan of *Sesbania bispinosa* seeds is found in the endosperm of the seed, the endosperm was separated by mechanical procedure from the whole seed and the polysaccharide isolated by exraction and subsequent precipitation with ethanol. The procedure of isolating the polysaccharide directly from the endosperm, therefore, afforded the galactomannan with high purity. The polysaccharide thus obtained was further purified by fractional precipitation with ethanol and dialysis and dried under vacuum. The purified galactomannan was found to be homogeneous and had mol. wt (Mw) of 2.29×10^5 and $[\alpha]_D^{30}$ + 22 (0.5 water). Complete hydrolysis of the polysaccharide revealed the presence of D-galactose and D-mannose. The ratio of constituent sugars was determined by HPLC of hydrolysate and on the basis of ^{13}C-NMR results and methylated sugars proportion. The results are reported in Table 1. The lower proportion of mannose in methylation studies may be either due to slight undermethylation of the compact mannan backbone resulting in the undetectable monomethylated mannose or due to alkaline degradation of the polymer. This phenomenon has been reported in other galactomannans[4].

To ascertain structural features, the galactomannan of Dhaincha seed was fully methylated by the Hakomori method[5] followed by the Purdie method[6]. The permethylated polysaccharide was hydro-

Table 1—Constituent sugar analysis of *Sesbania bispinosa* seed galactomannan

Sugar	HPLC	^{13}C-NMR data	Methylation studies
D-galactose	1.0	1.0	1.0
D-mannose	1.90	1.88	1.80

†NBRI Publication No. 352 (N.S.)
‡Indian Institute of Chemical Biology, Jadavpur, Calcutta 700 032

Table 2—Methylation analysis of the galactomannan

Methyl sugar*	T†		Molar proportion
	I	II	
2,3,4,6-Tetra-O-methyl-D-galactose	1.17	1.15	1.0
2,3,6-Tri-O-methyl-D-mannose	2.05	1.98	1.8
2,3-Di-O-methyl-D-mannose	4.08	4.52	1.0

*The methyl sugars were identified as the corresponding alditol acetates.
†Retention times are relative to 1,5-di-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucitol, on columns I (3% OV-225) and II (3% ECNNS-M).

lysed with 85% formic acid and then with 0.25 *M* sulphuric acid. The alditol acetates[7] of the methylated hydrolysate were identified and their relative molar proportions determined by GC (Table 2).

During ^{13}C-NMR studies of the galactomannan, the resonance of all the carbon atoms were fully resolved and readily identified, and the galactose : mannose ratios calculated from the measurements of the ratio of the corresponding peak-areas were in good agreement with those of chemical analysis. In the 75 MHz spectra (Fig. 1), C-1 (man) appeared as two (almost completely resolved) signals, 101.324 and 101.203 ppm, which were respectively assigned to non-substituted and substituted Man units (Table 3). The relative areas of the signals for C-1 (Gal) and

Table 3—Assignment of peaks in the ^{13}C-NMR spectra of *Sesbania bispinosa* seed galactomannan

Type of units	Chemical shifts					
	C-1	C-2	C-3	C-4	C-5	C-6
α-D-Galactopyranose	100.148	69.839	70.859	70.702	72.545	62.544
β-D-Mannopyranose unbranched at O-6	101.324	71.332	72.788	78.058	76.389	61.967
β-D-Mannopyranose branched at O-6	101.203	71.332	72.788	78.287	74.725	67.906

C-1 (Man, substituted and non-substituted) yielded the molar fraction of the two monomers presented in Table 2.

Both C-2 (Man) and C-3 (Man) showed two well resolved lines. The C-4 (Man) pattern of lines was similar to NMR pattern of guaran reported by Grasdalen and Painter[8]. It contained three almost completely resolved lines (Fig. 2). It is assumed that the resonance of C-4 of the branched and non-branched β-1,4 linked mannose units are sensitive, not only to nearest neighbour but also to other structural details. Due to the fact that substituted mannose units are branched at O-6, the resonances of their C-6 and C-5 are shifted 5.94 ppm downfield and 1.66 ppm upfield to the corresponding resonance of unbranched mannose units, respectively, and therefore, these resonances were readily identified. Likewise, carbon resonances of the D-galactose

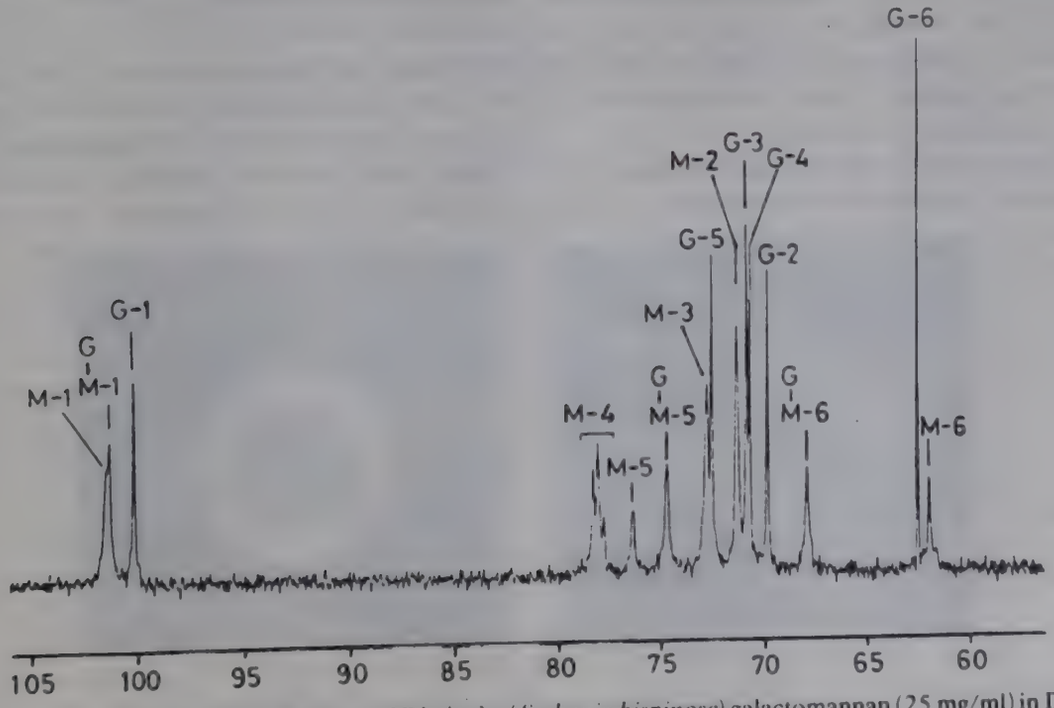


Fig. 1—^{13}C-NMR spectrum (75 MHz) of a solution of Dhaincha (*Sesbania bispinosa*) galactomannan (25 mg/ml) in D_2O (M = Mannose; G = Galactose)

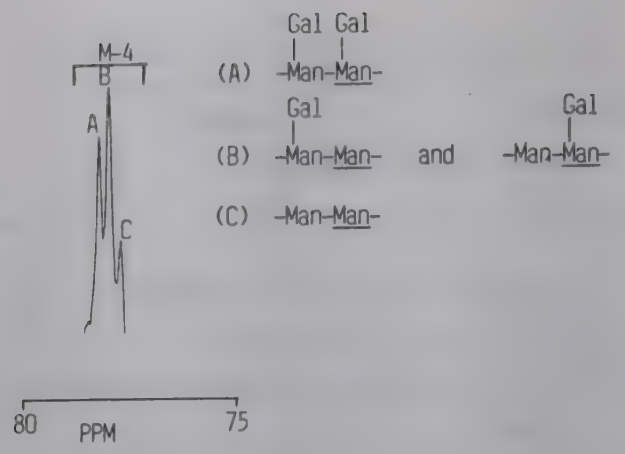


Fig. 2—^{13}C-NMR spectral region at 75 MHz of C-4 (Man). A, B and C are the probable interpretations

units accorded well with those reported for α-D-monomeric galactopyranose[9].

X-ray diffraction (Fig. 3) of the galactomannan had shown the same type of X-ray pattern as found in guar (Gal : Man ratio, 1.0 : 1.84) having galactose units (1→6) α-linked to the (1→4)-β-D-mannose backbone. These studies revealed the lower degree of crystallinity of the galactomannan.

The isolation of the three cleavage fragments from the methylated polysaccharide indicated its branched character and non-reducing terminals units, and also demonstrated that D-galactose and D-mannose units are in the pyranose form. Since 2,3,6-tri-O-methyl-D-mannose is the major component, the main chain must be composed of (1→4) linked D-mannose units out of which branched mannose units which give rise to 2,3-di-O-methyl-D-mannose, would be attached to non-reducing galactose units at C-6. Isolation of 2,3,4,6-tetra-O-methyl-D-galactose indicates that branches of galactose units are attached to the main chain of mannose through 1→6 linkage.

On periodate oxidation, the galactomannan consumed 1.35 moles of periodate for each hexose unit, with the concomitant liberation of 0.37 mole of formic acid. The periodate-oxidised galactomannan was reduced with $NaBH_4$. PC of hydrolysate revealed the presence of glycerol and erythritol. Traces of mannose were also detected. The glycerol and erythritol were found to be in a molar ratio of 1 : 1.85.

The IR spectrum of the purified polysaccharide showed absorption bands at 815 and 875 cm^{-1} indicating the presence of α-linked D-galactopyranosyl and β-linked D-mannopyranosyl units respectively[10].

Mild hydrolysis of the polysaccharide solution (2% in H_2O) with 0.04 *N* oxalic acid released only galactose. The resulting galactomannan after 5 hr had a galactose : mannose ratio of 1 : 2.2. The decrease in galactose contents was attributed to the fact that galactose residues are α-linked, since these are more labile than β-linked mannose units. The occurrence of α-D-galactose residues as branch points in the galactomannan from the seed of *Sesbania bispinosa*, was further confirmed by the fact that α-galactosidase from green coffee beans reacted with the galactomannan.

From the observations obtained so far, a simple symmetrical structure as represented by I could be proposed. This consists of a repeating unit with two β-(1→4) linked D-mannopyranose units in the main chain with branching at one of the two units of D-mannose at C-6, glycosidically linked by α-D-galactopyranose. Similar structures have been proposed earlier for the galactomannans of *Sesbania aegyptiaca*[12], *S. grandiflora*[13], *Delonix regia*[14], *Gladitsia triacanthos*[15] and *G. amorphoides*[11]. The results of periodate oxidation studies are in good agreement, as the theoretical value expected from the proposed structure is the consumption of 1.36 moles of periodate with the liberation of 0.37 mole of formic acid per anhydrohexose unit. The larger proportion of erythritol released upon hydrolysis of

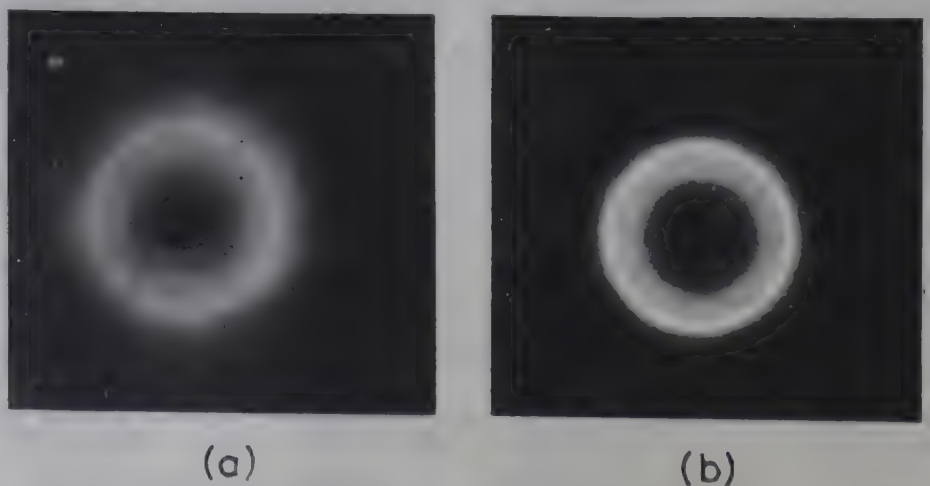
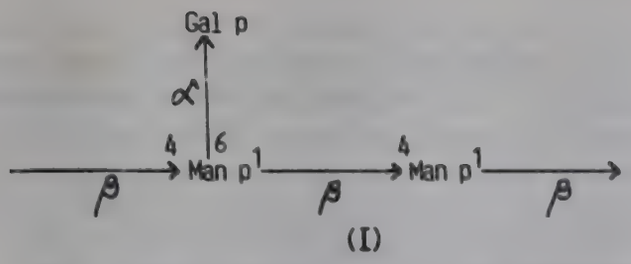


Fig. 3—X-ray diffraction pattern for (a) Dhaincha (*Sesbania bispinosa*), and (b) guar (*Cyamopsis tetragonotoba*) galactomannans



(I)

Man p = D-Mannopyranose; Gal p = D-Galactopyranose

polyalcohol of polysaccharide served as an evidence that the main polymeric linkage is of 1 → 4 type. The terminal galactose units released glycerol. The ratio of erythritol to glycerol indicates that the branching on the mannose occurs on an average of one in two units. The fact that only traces of mannose survived periodate oxidation indicates that no significant amounts of 1 → 3 linkage are present. It may be stated here that the seed galactomannans from *S. sesban*[12] (Syn. *S. aegyptiaca*) and *S. grandiflora*[13] as reported previously showed a galactose : mannose ratio of 1 : 1.67 and 1 : 1.8 respectively. None of them contained any 1 → 2 or 1 → 3 linked mannose. Thus, all the three *Sesbania* species galactomannans worked out so far, appear to be more or less similar in their structure.

Experimental procedure

All evaporations were carried out under reduced pressure at 40° and specific rotations are equilibrium values as recorded on Automatic Polarimeter modelAA-10 (Optical Activity, London). Decending PC was performed on Whatman No. 1 and 3 MM sheets with the solvent systems : (a) *n*-butanol-acetic acid-water (4:1:5), (b) benzene-ethanol-water (167:47:15), and (c) *n*-butanol-ethanol-water (31:11:9). Sugars were detected with acid aniline phthalate and alcohols were sprayed with acetonic silver nitrate followed by 1% alc. sodium metaperiodate and alc. sodium hydroxide, GC-FID/TCD analysis was conducted using glass column (1.83cm × 6mm) containing (I) 3% OV-225 on Gas Chrom Q (100-120 mesh) and (II) 3% ECNSS-M on Gas Chrom Q (100-120mesh), oven temp. 170°, detector temp. 250°, inj. temp. 200° and N_2 flow 50ml/min. A reporter integrator 3390A (Hewlett & Packard) was used to determine molar ratio. Gel filtration chromatography was performed on Bio-Gel P2 (200-400 mesh) analytical column 1.5 × 200 cm with water as eluant at 65°. HPLC analysis was carried out with Waters Associates Model R-401 using column CHO-682 from Interaction Chemicals Inc. (USA). Differential Refractometer model R-401 was used for analysis. X-ray diffraction studies were carried out on 1 mm × 8 mm films glued on metallic disc using nickel filtered CuK_α radiation from Philips sealed tube generator and Siemen Model F K60-04 Camera. Diffraction patterns were recorded on a Kodak No-screen film.

For ^{13}C-NMR spectroscopy, the sample was dissolved in D_2O (25mg/ml) and spectra were recorded on a Bruker AM 300 instrument equipped with an Aspect 3000 computer at 75 MHz. All experiments were performed in the Fourier-transform mode. Repetition time was 0.7 sec and effective flip angle was 60°. A probe temp. of 68° was used to diminish tembling ratio. The spectra were recorded at 16 K data points with a digital resolution of 1.2 Hz/Pt. An accumulation of 12964 transients was required, according to the concentration of the solution. All the signals are referred to SR which has been defined by using deuterated acetone in D_2O. IR spectra were recorded in $CHCl_3$ or KBr pellets. The viscosities (cP) were determined by Brookfield Synchro-Lectric Viscometer models RVT and LVT at 20 rpm and 30 rpm respectively using proper spindles. Amberlite IR-120 (H^+) and IR-45 (OH^-) resins were used for deionization. Colorimetric measurements were recorded on an EC spectrophotometer GS 866 B at 570 nm. Molecular weight ($M\bar{w}$) of the galactomannan, dissolved in distilled water (1 mg/2ml) and filtered through 0.45 nm millipore membrane, was determined on a Waters Millipore model 150-C ALC/GPC.

Isolation and purification

The endosperms were separated from the thoroughly cleaned and washed seeds (100 g) by mechanical means and dried at room temperature and then in oven at 45°, yield 36.3%, ash 0.35%, crude protein 8.5%, pentosan 1.09%, fat 0.5% and crude fibre 1.9%. The powdered endosperm (gum) had the viscosity for 1% solution in the range of 400 to 1200 cP depending on the mesh size and moisture content. Similarly for 2%, the range was of the order of 3000 to 15000 cP. The Dhaincha gum sample with a mesh size of 100 was interacted with Xanthan in varying ratio. None of the interacted solutions produced a rubbery gel thus indicating the higher galactose content in the Dhaincha galactomannan. However, a 1% solution of Xanthan and Dhaincha gum with 0.5 : 0.5 ratio considerably increased the viscosity which ranged from 2350 to 4500 cP, again depending on the type (mesh) of Dhaincha gum used. Viscosity behaviour of Dhaincha gum at different conditions of pH, concentration, temperature, time, etc. and its interaction with Xanthan gum at different concentrations have already been reported[16,17] by the authors. The endosperm (35 g) was suspended in 1 litre H_2O overnight, then heated on a boiling water-bath for 5 hr. The swollen endo-

sperms were homogenized with hot water and the viscous solution (2.5 l) was filtered through muslin cloth and centrifuged. The solution was added to 5.2 litre of ethanol resulting in the precipitation of the polysaccharide which was collected and dried (yield 23.5 g). This dried material was redissolved in water (3.6 l) and dialysed in running tap water. The polysaccharide was repurified by dissolving in water and precipitation with 70%, 80%, 90% and 95% ethanol. The white amorphous powder thus obtained (yield 19.2 g) did not reduce Fehling's solution. Nitrogen, sulphur, halogens and uronic acids were absent. It had no pentose. Preliminary analysis gave $[\alpha]_D^{30}$ + 22.0° (0.5 H_2O) and sulphated ash 0.14%. The weight average molecular weight ($M\bar{w}$) of the polysaccharide was 2.29×10^5.

Hydrolysis of the galactomannan

The polysaccharide (0.5 g) was kept with 72% sulphuric acid (3.5 ml) at 5° overnight, diluted with water (90ml) and refluxed on a boiling water-bath for 13 hr. The hydrolysate was neutralized, filtered and concentrated to a thin syrup. PC using solvent (a) revealed the presence of galactose and mannose.

Estimation of sugars

The polysaccharide (20 mg) along with myo-inositol (10 mg) (as internal standard) was hydrolysed with 2 ml of 2*N* sulphuric acid for 18 hr at 100° in a sealed tube. the hydrolysate was worked-up in the usual manner and analysed by HPLC with column CHO-682. The molar proportion of D-galactose and D-mannose was found to be 1 : 1.90.

Mild hydrolysis with oxalic acid

The polysaccharide (1 g) was dissolved in 50 ml water and added to it 25 ml of 0.04 *N* oxalic acid and the reaction mixture heated at 100°. Aliquots (10 ml) were withdrawn at intervals of 1 hr. Each aliquot was precipitated with ethanol (15 ml) and examined by PC using solvent (a). The supernatant liquid on PC showed the presence of galactose only. After 5 hr, the reaction mixture was precipitated with ethanol and the precipitated material hydrolysed with 1*N* sulphuric acid in a sealed tube for 18 hr. The hydrolysate was neutralized, deionised and concentrated. The sugars were converted to their alditol acetates and estimated by GC using column (ii). Myo-inositol was used as internal standard. The molar ratio of D-galactose and D-manose was found to be 1 : 2.2.

Methylation of the polysaccharide

The polysaccharide (20 mg; dried over P_2O_5) was dispersed in 2 ml of formamide by continuous stirring for 1 hr. Acetic anhydride (2 ml) and pyridine (2.5 ml) were added to the disperion which was stirred for 16 hr at room temperature. The reaction mixture was cooled and water (10 ml) added to it dropwise. The mixture was dialysed against water, concentrated and purified by passing through a column (30 × 15 cm) of Sephadex LH-20 which was irrigated with acetone. The eluant was monitored by polarimetry, the acetylated polysaccharide (15.5 mg) being eluted in the void vol.

The acetylated polysaccharide was methylated by the Hakomori method[10]. The material (10mg) was dissolved in dimethyl sulphoxide (5 ml) and treated with 2 *M* methylsulphinyl sodium (5 ml) under N_2. The gelatinous solution was agitated in an ultrasonic bath for 30 min and then kept at room temperature overnight. Methyl iodide (2 ml) was added dropwise with cooling and mixture was stirred for 2 hr, dialysed and lyophilized. The product was remethylated by the Purdie method[10]. The IR spectrum of fully methylated polysaccharide showed no OH bands, yield 9.2 mg. The fully methylated polysaccharide was hydrolysed with 85% formic acid at 100° and then with 0.25 *M* sulphuric acid at 100°. The methylated sugars were analysed by GC on columns (i) and (ii). The results and mol proportions of the methylated sugars are given in Table 1.

Periodate oxidation of the galactomannan

The polysaccharide (95 mg) was oxidised with 0.15 *M* sodium metaperiodate as mentioned earlier. After 74 hr the excess of periodate was destroyed with ethylene glycol and solution dialysed in running tap water for 10 hr. The solution was concentrated to 350 ml and reduced with sodium borohydride (1.15 g) at room temperature for 20 hr. The solution was neutralized with dil. formic acid, filtered, deionised and concentrated. After removing boric acid by repeated evaporation with methanol, the residue was dissolved in sulphuric acid (100 ml) and the solution heated for 12 hr. The hydrolysate was neutralized with barium carbonate, filtered, deionised and evaporated to a syrup. PC of the syrup using solvent (c) revealed the presence of glycerol, erythritol and traces of mannose. The mixture was separated on Whatman No. 3MM sheets using solvent (c).

Fraction I was identified as glycerol by conversion into glycerol tri-*p*-nitrobenzoate, m.p. 185.7°. Fraction II was identified as erythritol, m.p. 120°. It was converted into tetra-O-tosyl-erythritol m.p. 163-65°. The molar ratio of glycerol and erythritol, as determined by chromotropic method[19], was 1 : 1.85.

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Synthesis and QSAR of 1-aryl-4-(β-2-quinolyl/l-isoquinolylethyl)piperazines and some related compounds as hypotensive agents[†‡]

Aruna Murti, Kalpana Bhandari, Siya Ram, Yenamandra S Prabhakar, Anil K Saxena, (Late) P C Jain, Anil K Gulati, R C Srimal, B N Dhawan, S Nityanand & Nitya Anand*

Central Drug Research Institute, Lucknow 226 001

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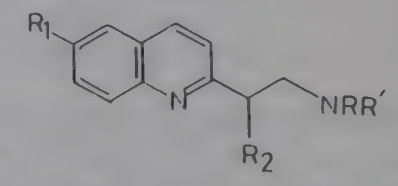
1-Aryl-4-(β-2-quinolylethyl)piperazines (**7-27**, **44**, **45**) have been prepared by the condensation of 2-alkenylquinolines and 1-arylpiperazines. The corresponding 1-aryl-4-(β-hydroxy-β-2-quinolylethyl)piperazines (**34-41**) have been prepared by the condensation of 2-bromoacetylquinoline with 1-arylpiperazines followed by LAH reduction of the 2-substituted acetylquinolines thus obtained. The 4-quinolylethyl (**47-51**) and 1-isoquinolylethyl (**53-57**) analogs have been prepared by the condensation of 4-methylquinoline and 1-methylisoquinoline with the appropriate piperazines/amines and formaldehyde under Mannich conditions. Most of the compounds exhibit prominent hypotensive activity and weak to moderate diuretic, antiinflammatory and CNS depressant activities. A QSAR study for hypotensive activity, has been carried out and the best correlation is described by the parabolic relationship between logP and hypotensive activity (with logPo = 4.23). Amongst the compounds studied, the centrally acting hypotensive 1-(3-methylphenyl)-4-(β-2-quinolylethyl)piperazine (**17**) is found to possess the most suitable profile of hypotensive activity.

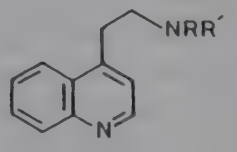
In view of the common occurrence of 1-arylpiperazine and β-arylethylamine substructures in clinically useful CNS and/or CVS agents[1-3], some selected 1-aryl-4-(β-2-quinolylethyl)piperazines were synthesized and found to possess significant hypotensive activity. This led us to investigate (i) site and mode of action of these compounds and (ii) structure function relationship of this group of compounds and some related structures. The results are presented in this paper.

Attempted preparation of 1-(3-methylphenyl)-4-(β-2-quinolylethyl)piperazine (**17**) by Mannich reaction of quinaldine with the piperazine and formaldehyde gave the required product but in less than 10% yield. Therefore, such compounds were prepared through the corresponding 2-vinylquinoline (**5**), prepared according to the literature method[4] starting from quinaldine (**1**). Condensation of **1** with a variety of piperazines led to the corresponding 1-aryl-4-(β-2-quinolylethyl)piperazines (**7-27**) (Table 1). The morpholino compound (**21**) on catalytic hydrogenation over Pt yielded the tetrahydroquinoline derivative (**28**) (Scheme 1).

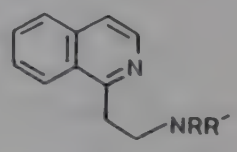
2-Bromoacetylquinoline (**32**) was required for the synthesis of the corresponding β-hydroxy-β-(2-quinolyl)ethyl analogs. Its synthesis according to the literature method[5] gave poor yield and it was found more convenient to prepare it from quinaldic acid by Arndt-Eistert reaction as described in Scheme 2. 2-Bromoacetylquinoline (**32**) on condensation with various amines/piperazines yielded the ketones (**33**) which were found to be rather unstable and were reduced with $LiAlH_4$ without isolation to provide the required compounds (**34-41**). In the PMR spectrum of these compounds the *HC* (OH) appeared as a quartet at 4.49 with $J_{A,X} = 9$ and $J_{B,X} = 5$ Hz showing nonequivalence of H_A and H_B.



3, 7-24, $R_1 = H$; $R_2 = H$
4, 25-27, $R_1 = OCH_3$; $R_2 = H$
34-41, $R_1 = H$; $R_2 = OH$
44-45, $R_1 = H$; $R_2 = CH_3$



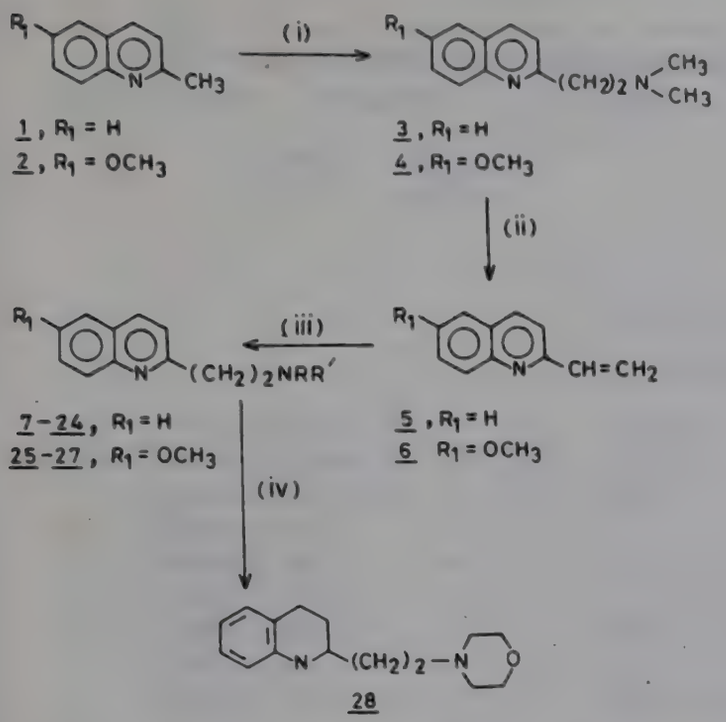
47-51



53-57

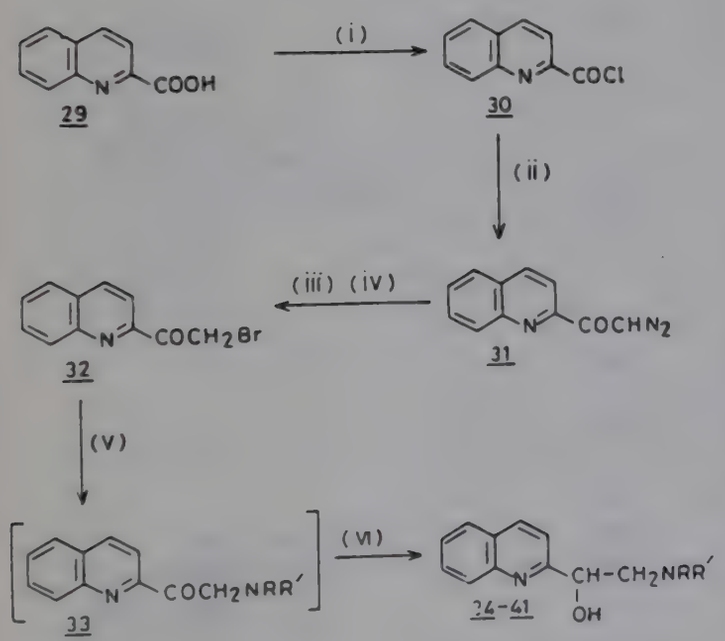
1-Aryl-4([α-methyl-β-(2-quinolyl)ethyl]piperazines (**44, 45**) were synthesized from 2-isopropenylquinoline (**43**), which in turn was obtained form

[†]CDRI Communication No. 4432.
[‡]Dedicated to the memory of (Late) Prof. E. Lederer.



(i) $HCHO/HN(CH_3)_2$; (ii) $(CH_3)_2SO_4/Et_3N$; (iii) Amines/ piperazines/ morpholine / piperidine, absolute alcohol, glacial AcOH; (iv) Pt/H_2

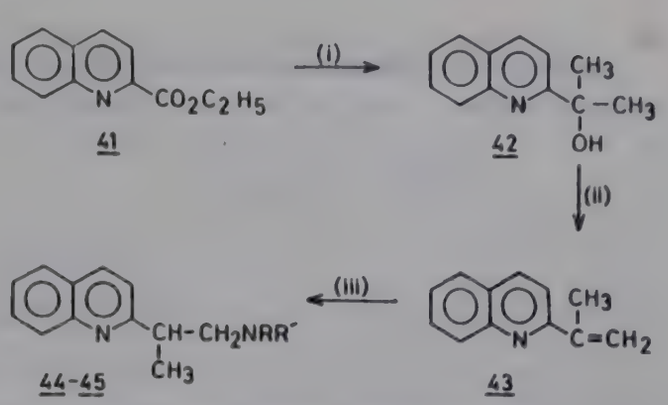
Scheme 1



(i), $SOCl_2$; (ii), CH_2N_2/ether, (iii), 40% HBr; (iv), 1N $NaHCO_3$; (v), HNRR′; (vi) $LiAlH_4$.

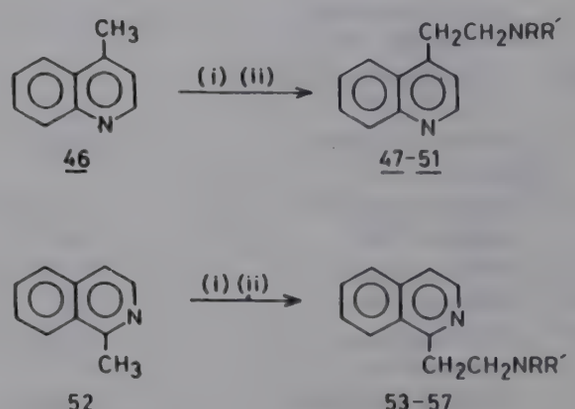
SCHEME 2

2-ethyl quinaldate (**41**) (Scheme 3), Compound **41** on treatment with methylmagnesium iodide gave 1-α-quinolylisopropanol (**42**), which could not be dehydrated by concentrated sulfuric acid[6] to (**43**). However, treatment of **42** with thionyl chloride in



(i) CH_3MgI (ii) $SOCl_2$/pyridine (iii) HNRR′

Scheme 3



(i) HCHO; (ii) HNRR′.HCl

Scheme 4

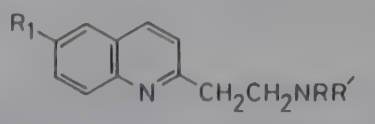
pyridine gave **43**, which on condensation with appropriate piperazines yielded the required **44, 45**.

The 4-β-quinolylethylamines/piperazines (**47-51**) and 1-β-isoquinolylamines/piperazines (**53-57**) were synthesized from 4-methylquinoline (**46**) and 1-methylisoquinoline (**52**) respectively by reacting them with appropriate amines/piperazines and formaldehyde under Mannich conditions (Scheme 4).

Pharmacological activity

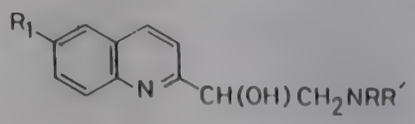
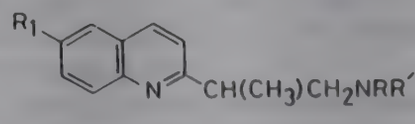
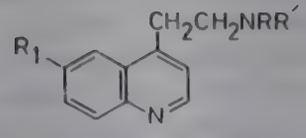
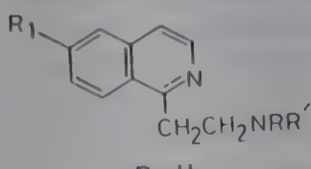
The compounds were tested for their acute toxicity (LD_{50}), gross behavioural effects, reduction in spontaneous and forced locomotor activities, antagonism to amphetamine hyperactivity and amphetamine toxicity in aggregated mice and electroshock seizures in male mice. The effects on conditioned and unconditioned responses (CAR and UCR) were determined in rats at 1/5th of LD_{50} dose by standard methods described earlier[8]. Effect on blood pressure and respiration was studied on anaesthetized (pentobarbitone, 40 mg/kg i.p.) cats by administering 2.85 μmol/kg i.v. of the compounds. The compounds were evaluated for antiinflammatory activity[9] against carageenin-induced oedema in mice and

Table 1—Characterisation data and biological responses of compounds **3-27, 34-41, 44, 45, 47-51** and **53-57**

Compd	NRR′	m.p. (°C)	Mol. formula	LD_{50} mg/kg	BP response		Other activities
					Hypotension (mm Hg)	Duration (min)	
							
	R_1=H (3-24); R_1=OCH_3 (25-27)						
3	N,N-dimethylamino	90	$C_{13}H_{18}N_2Cl_2$		14	3	—
7	4-phenylpiperazine-1-yl		$C_{21}H_{23}N_3$	600	52	75	—
8	4-(2,4-dimethylphenyl) piperazin-1-yl 2HCl		$C_{23}H_{29}Cl_2N_3$	300	16	60	Diuretic 65 (75)
9	4-(3-trifluoromethyl phenyl)piperazin -1-yl	94	$C_{22}H_{22}F_3N_3$	800	48	80	Diuretic 105 (130)
10	4-(3,4-dichlorophenyl) piperazin-1-yl	88	$C_{21}H_{21}N_3Cl_2$	800	13	22	Diuretic 53 (200)
11	4-(3,4-dimethylphenyl) piperazin-1-yl	108	$C_{23}H_{27}N_3$	800	60	65	Diuretic 87 (50)
12	4-(4-chlorophenyl) piperazin-1-yl		$C_{21}H_{22}ClN_3$	200	30	45	
13	4-(4-fluorophenyl) piperazin-1-yl	84	$C_{21}H_{22}FN_2$	300	70	70	
14	4-(3-fluorophenyl) piperazin-1-yl		$C_{21}H_{22}FN_3$	600	60	80	
15	4-(2,5-dimethylphenyl) piperazin-1-yl		$C_{23}H_{27}N_3$	150	16	21	Diuretic 100 (37.5); AI 20 (30)
16	4-(2-methoxyphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_{30}$	200	80	300	Diuretic 74(50); AiI 13.3 (40)
17	4-(3-methylphenyl) piperazin-1-yl		$C_{22}H_{25}N_3$	800	78	110	Diuretic 96 (150) nictating membrane 65 (0.1)
18	4-(2-chlorophenyl) piperazin-1-yl		$C_{21}H_{22}ClN_3$	800	54	70	
19	4-(3-chlorophenyl) piperazin-1-yl	97	$C_{21}H_{22}ClN_3$	800	58	70	AI 24 (200)
20	N-methyl, N-benzylamino	oil	$C_{19}H_{20}N_2$	200	30	3	
21	morpholin-1-yl		$C_{15}H_{18}N_2O$	200	84	6	
22	4-methylpiperazin-1-yl		$C_{16}H_{21}N_3$	200	24	Tr	Diuretic 80 (50; amph. hyper activity[1] 22 (40)
23	4-(2-fluorophenyl) piperazin-1-yl	86	$C_{21}H_{22}FN_3$	600	30		
24	4-(2-phenylethyl) piperazin-1-yl	oil	$C_{23}H_{27}N_3$	600	1		
25	4-phenylpiperazin-1-yl	106-7	$C_{22}H_{25}N_3O$		40	95	
26	4-(3-methylphenyl) piperazin-1-yl	86	$C_{23}H_{27}N_3O$		60	70	Nictating membrane 66 (0.1)
27	4-(4-methylphenyl) piperazin-1-yl	120-21	$C_{23}H_{27}N_3O$		64	100	

(*contd.*)

Table 1—Characterisation data and biological responses of compounds **3-27, 34-41, 44, 45, 47-51** and **53-57**—*Contd*

Compd	NRR′	m.p. (°C)	Mol. formula	LD_{50} mg/kg	BP response		Other activities
					Hypotension (mm Hg)	Duration (min)	
							
			$R_1 = H$				
34	4-phenylpiperazin-1-yl	127	$C_{21}H_{23}N_3O$	300	30	Tr	AI 15 (60)
35	4-methylpiperazin-1-yl	oil	$C_{16}H_{21}N_3O$	300	1		AI 34.8 (60)
36	4-(4-methoxyphenyl) piperazin-1-yl	105	$C_{22}H_{25}N_3O_2$		30	40	
37	4-(4-fluorophenyl) piperazin-1-yl	oil	$C_{21}H_{22}FN_3O$		32	93	
38	4-(2-methylphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_3O$		40	80	
39	morpholin-1-yl	oil	$C_{15}H_{18}N_2O_2$	800	12	5	Diuretic 85 (200). AI 20 (160)
40	piperidin-1-yl	oil	$C_{16}H_{20}N_2O$	300	10	10	PCA[g] 58 (60)
41	m-tolylpiperazin-1-yl	118	$C_{22}H_{25}N_3O$	800	50	90	AI 33.4 (200)
							
			$R_1 = H$				
44	4-phenylpiperazin-1-yl	oil	$C_{22}H_{25}N_3$	300	50		
45	4-(m-tolyl)piperazinyl	oil	$C_{23}H_{27}N_3$	800	40	180	Rotarod fall out[h] (200); amphi Hyper 49 (200) hypothermia 2 (200)
							
			$R_1 = H$				
47	4-phenylpiperazin-1-yl	oil	$C_{21}H_{23}N_3$	75	1		AI 19 (15)
48	morpholin-1-yl	oil	$C_{15}H_{18}N_2O$	400	10	5	
49	piperidin-1-yl	oil	$C_{16}H_{20}N_2$	75	24	5	AI 18 (15)
50	4-(2-methylphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_3$	400	20	65	
51	4-(m-methylphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_3$	800	24	Tr	
							
			$R_1 = H$				
53	4-phenylpiperazin-1-yl	oil	$C_{21}H_{23}N_3$	400	0	0	PCA 59 (80), AI 59 (80)

(*contd.*)

Table 1—Characterisation data and biological responses of compounds **3-27, 34-41, 44, 45, 47-51** and **53-57**—*Contd*

Compd	NRR'	m.p. (°C)	Mol. formula	LD_{50} mg/kg	BP response		Other activities
					Hypotension (mm Hg)	Duration (min)	
54	morpholin-1-yl	oil	$C_{15}H_{18}N_2O$	300	0	0	
55	piperidin-1-yl	oil	$C_{16}H_{20}N_2$	150	22	2	
56	4-(2-methylphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_3$	200	16	10	CAR[h] 60 (40) amph. Hyper 72 (40). hypothermia 3 (40)
57	4-(3-methylphenyl) piperazin-1-yl	oil	$C_{22}H_{25}N_3$		0	0	Diuretic 92 (100)

(a) Approximate LD_{50} mg/kg ip (mice)
(b) Fall in blood pressure in mm of Hg, duration in min
(c) Figures in parentheses indicate dose in mg/kg
(d) Diuretic activity (oral); figures in parentheses describe dose in mg/kg
(e) Antiinflammatory activity against carageenin-induced oedema in mice
(f) Amph. hyper.: % Reduction in amphetamine-induced hyperactivity
(g) PCA refers to prevention of passive cutaneous anaphylaxis
(h) % Conditioned avoidance response in rats.

diuretic activity[10] (chlorothiazide as standard) in rats at 1/5th LD_{50} dose. The significant results are summarised in Table 1.

The compound showing maximum hypotensive activity was also tested in renal hypertensive and spontaneously hypertensive rats. The blood pressure was measured by tail cuff method[11]. The central hypotensive effect of such a compound was investigated by the methods described elsewhere[12].

The compounds were, in general, well tolerated and showed weak to moderate depressant action on gross behaviour. Most of these compounds showed good hypotensive activity, among these **11**, **12** and **23** caused tachyphylaxis. It was observed that introduction of a hydroxy group at α-position maintained the hypotensive activity e.g. in compounds **34-41**. A similar pattern was shown by introduction of a methyl group at the α-position (**44, 45**). The corresponding 4-quinolyl substituted compounds **47-51** were also active but 1-isoquinolyl derivatives (**53-57**) were inactive.

In addition, some of these compounds showed other activities such as antiinflammatory (**15, 16, 34, 35, 39, 41, 47, 49, 52**), diuretic (**8, 9, 10, 11, 15, 16, 17, 22, 39, 56**) and anti-PCA (**40, 52**).

Biological activity of **17**

The most active hypotensive compound of the series was 1-(3-methylphenyl)-4-[β-2-quinolylethyl]piperazine (**17**) which has been evaluated in greater detail and some of the results are described below.

(1) Cardiovascular activity: Compound **17** lowered the blood pressure and the heart rate of anaesthetised as well as unanaesthetised (decerebrate) cats. It produced a hypotension of 25% for about 1 hr at a dose of 0.1 mg/kg i.v. Higher doses produced greater effect for longer duration (Table 2). It was well absorbed from the gastrointestinal tract. Compound **17** produced an antihypertensive effect when administered to renal hypertensive and spontaneously hypertensive rats either as a single dose or as single daily dose for 15 days. The antihypertensive effect did not decrease on chronic administration of the compound (Table 3).

(2) Effect on heart and vascular resistance: Compound **17** had no significant effect on the contractility of heart at hypotensive doses. Higher doses (more than 1 mg/kg i.v.), however, had a negative inotropic effect. It reduced the cardiac output by 16.4% at a dose of 0.1 mg/kg i.v. and at the same

Table 2—Hypotensive activity of compound **17** in cat

Preparation	Dose (mg/kg)	Hypotension (%)	Duration (min)
Normal	0.1 i.v.	24.8 ± 8.7	63.1 ± 9.4
	0.5 i.v.	68.9 ± 12.6	3.3 ± 28.3
	1.0 i.v.	51.0 ± 6.5	> 110
	1.0 i.v.	39.1 ± 6.1	> 110
Spinal transected	1.0 i.v.	22.3 ± 15.2	21.4 ± 19.5
Decerebrate	1.0 i.v.	55.6 ± 6.9	74.75 ± 4.2

Table 3—Antihypertensive activity of compound **17** in rat

Dose (mg/kg po)	Hypotension (%) at				
	1 hr	3.5 hr	24 hr	48 hr	15th day
Renal hypertensive					
0.5	16.9	7.4			
1.0	20.1	11.4			
Spontaneously hypertensive					
1.0		24.2	12.4	27.0	24.8
2.5	24.4	34.0			
5.0	33.3	16.0			

dose level peripheral resistance was decreased by 16% in cat.

(3) Mechanism of action: The compound did not have any significant effect when administered to spinal transacted cats but the effect was present in decerebrate animals (Table 1). This indicated a central site of action. Moreover, a lower dose of 5-10 μg, when administered into a vertebral artery, produced hypotension. When **17** was applied topically over the exposed ventral surface of medulla as a 0.05% solution, it produced significant hypotension. The excitability of the vasomotor area of medulla was also reduced further supporting our contention of central site of action for hypotensive activity.

(4) Effect on central nervous system: Compound **17** had a depressant effect on the gross behaviour of mice and rats. It antagonised amphetamine-induced hyperactivity as well as toxicity. The acute LD_{50} in mice was 957.4 mg/kg i.p. and in rats it was more than 1000 mg/kg i.p.

(5) Miscellaneous effects: Compound **17** also had weak diuretic activity (98% activity of chlorothiazide at 125 mg/kg). It had a nonspecific spasmolytic effect on guinea pig ileum at a dose level of 10 μg/ml.

Quantitative structure-activity analysis (QSAR)

In view of the marked hypotensive activity exhibited by these compounds, the role of physicochemical parameters in determining the activity was analysed in terms of electronic (σ, Swain and Luptons resonance R and polar F), steric (MR) and hydrophobic (log P) properties through a quantitative structure activity analysis. As the 4-substituted quinoline analogs and the isoquinoline derivatives were less potent than the corresponding 2-substituted quinolines the former have not been included in the analysis. Further, five compounds, viz. **11**, **12**, **13**, **21** and **39** showed tachyphylaxis and were, therefore, not considered in the analysis. It is clear from the correlation matrix between independent physicochemical parameters and dependent hypotensive activity (described as log blood pressure fall) that none of independent parameters has correlation coefficient 0.39 with hypotensive activity. None of the independent parameters has intercorrelation > -0.4 except log P and MR with intercorrelations ($r = 0.6$) and ($r = 0.72$), respectively.

Attempts to correlate combination of non-collinear parameters with the hypotensive activity were unsuccessful as the correlation coefficient was 0.6 and results were statistically insignificant. The correlation for the total set of 25 compounds was described by the parabolic relationship between log P and hypotensive activity (Eq. 1) where n is the number of data points, r is correlation coefficient, s is standard deviation and F is the test for statistical significance of regression.

$$\log \text{BP fall} = 1.559\ (0.353) \log P - 0.196\ (0.046) \log P^2 - 1.401 \quad \ldots (1)$$
$$(n = 25; r = 0.693; s = 0.195; F = 10.14)$$

In Eq. (1), the values within parentheses describe standard error of the regression coefficient. Though the Eq. (1) is statistically significant [F_2, 22 ($= 0.01$) $= 5.72$ F_2 22 $= 10.14$] it explains only 48% of the variance. After removing two other compounds **3** and **22**, former having N,N-dimethyl group instead of piperazine and the latter having methyl group at piperazine N instead of aryl group as present in majority of the compounds, the new Eq. (2) describing the parabolic dependence of hypotensive activity with logP was highly significant with high correlation coefficient ($r = 0.940$), low standard deviation ($s = 0.09$) and high statistical significance [F_2, $20 = 75.74$, F_2, $20(\alpha = 0.001) = 5.85$]. The regression coefficients logP and $(\log P)^2$ were also significant as shown by the standard error of regression coefficient.

$$\log \text{BP fall} = 4.789\ (0.391) \log P - 0.569\ (0.046) (\log P)^2 - 8.269 \quad \ldots (2)$$
$$(n = 23; r = 0.940; s = 0.09; F = 75.74)$$

Further, Eq. (2) predicts the activity of both highly and weakly active compounds (Fig. 1). The parabolic dependence is justified in whole animal system where transport of the drug at the active site may be the rate-limiting step. This also corroborates our earlier findings in the QSAR of pyrazinoisoquinolines[14,15]. The ideal logP in these compounds would be $(\log P)_0 = 4.23$ which is almost being attained in compound **17**.

Experimental Procedure

All the compounds were routinely characterized by IR, PMR and elemental analyses. The IR spectra were recorded on a infracord 337 spectrophoto-

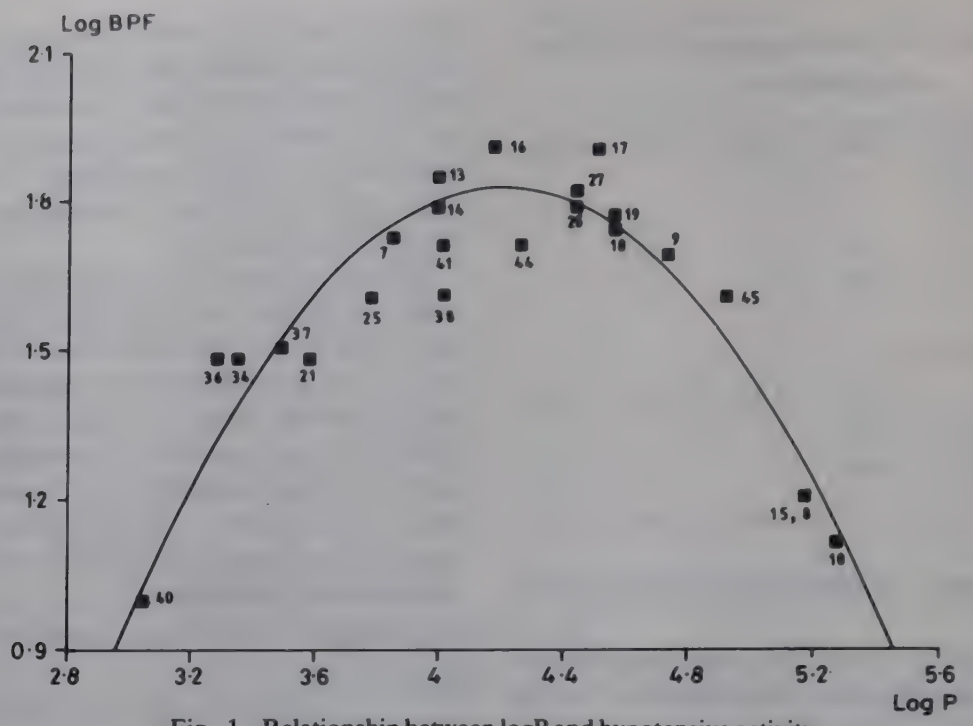


Fig. 1—Relationship between logP and hypotensive activity

meter, ν_{max} in cm^{-1} and PMR on aVarian A-60D instrument using TMS as an internal reference; chemical shifts are expressed in τ-scale. Mass spectra were recorded on a JEOL JMS D-300 instrument. Purity of the compounds was checked by TLC on silica gel or alumina plates and spots were located by spraying with $KMnO_4$ or keeping plates in iodine vapours. The melting points were determined in an electrically heated apparatus and are uncorrected. Analysis of each compound was found within ±0.4% of required value.

β-N,N-dimethylaminoethylquinaldine (**3**)

This was prepared according to the literature method, b.p. 110°/1 mm Hg (lit.[4] b.p. 150-57°/2-3 mm Hg; yield 40%. similarly, β-N,N-dimethylaminoethyl-6-methoxyquinoline was prepared in 30% yield and characterized as the hydrochloride salt, m.p. 94-95°.

2-*Vinylquinoline* (**5**)

It was prepared from **1** according to literature method, yield, 50%, oil b.p. 76°/1 mm Hg (lit.[4] b.p. 100-101°/2 mm Hg.

Similarly, 2-vinyl-6-methoxyquinoline was prepared, yield 50%, oil.

1-(3-*Methylphenyl*)-4-(*β*-2-*quinolylethyl*)*piperazine* (**17**)

A mixture of **5** (0.17 g, 0.001 mole), 3-tolylpiperazine (0.164 g, 0.001 mole) absolute ethyl alcohol (5 ml) and gl acetic acid (0.1-0.15 ml) was refluxed for 24 hr, concentrated, the residue diluted with water and treated with 10% aq NaOH (5 ml). The solid obtained was extracted with ethyl acetate (3 × 10 ml), dried (Na_2SO_4) and concentrated to give **17**, which was crystallized from hexane; yield 0.17 g, m.p. 82°; IR(KBr): 3000, 2850, 1620, 1510, 1460, 1440, 1390, 1350, 1310, 1260, 1190, 1150, 1055, 1010, 960, 840, 810, 770, 750, 690; UV (0.1N HCl): 210, 240, 320 nm; PMR (CCl_4): 1.75-2.82 (m, 7H, ArH), 3.25-3.5 (m, 3H, rest ArH), 6.1-7.14 (m, 8H, $N-CH_2$), 7.15-7.44 (m, 4H, $N-CH_2$, $-CH_2$), 7.75 (s, 3H, CH_3). MS = m/z 331.

Similarly, other compounds **7-27** were prepared by the condensation of appropriate piperazine/amines and vinylquinoline. Their physical data are described in Table 1.

Quinoline-2-*carboxychloride* (**30**)

It was prepared according to the reported method[7], yield 80%, m.p. 100° (lit. m.p. 97°).

2-*Quinolyl diazomethyl ketone* (**31**)

A solution of 2-chlorocarboxylquinoline (1.9 g, 0.01 mole) in dry ether (50 ml) was added dropwise to a stirred solution of diazomethane (0.25 g, 0.03 mole) in dry ether during 1 hr at 0°C. The reaction mixture was kept at 0° for 12 hr, ether removed and the residue dried under reduced pressure to give **31**, yield 2 g (100%), m.p. 65-66°; IR (KBr): 2090, 1594, 768; PMR ($CDCl_3$): 1.64-2.44 (m, 6, ArH), 3.04 (s, 1, $COCHN_2$).

2-*Bromoacetylquinoline* (**32**)

Hydrobromic acid (1.4 ml; 48%) was added to a

stirred solution of **31** (1.95 g, 0.01 mole) in dry ether (50 ml) at 0° and stirred for 1/2 hr. The reaction mixture was neutralised with aq $NaHCO_3$, the ether layer separated, dried (Na_2SO_4) and evaporated to give **32**, yield 1.95 g (80%), m.p. 125-26° (lit.[5] m.p. 125°). IR(KBr): 1711 (C=O), 1600 (aromatic), 750 (phenyl); PMR ($CDCl_3$): 1.6-2.37 (m, 6, ArH), 4.94 (s, 2, $COCH_2Br$).

1-(*β-2-Quinolyl-β-hydroxyethyl*)*piperidine* (**40**)

A solution of **32** (2.5 g, 0.01 mole) in dry benzene (60 ml) was added dropwise to stirred solution of piperidine (1.7 g, 0.02 mole) in dry benzene (50 ml) at 0°-5°C. The reaction mixture was filtered and the filtrate concentrated to get 2-(piperidinylmethyl) carboxyquinoline (**33**), yield 2.54 g. This compound was dissolved in dry THF (60 ml) and added dropwise to a stirred suspension of LAH (2 g) in dry ether (50 ml) under N_2 atmosphere, refluxed for 4 hr, kept overnight, cooled, and excess of LAH decomposed by successive addition of water and aq NaOH. The reaction mixture was filtered and evaporated to give **40** as an oil which was purified by chromatography over neutral alumina column using benzene containing increasing proportions of ethyl acetate as eluents to give pure **40**, yield 1.5 g (50%), m.p. 127°; IR(KBr): 2900, 760; PMR($CDCl_3$): 1.67-2.67 (m, 6, H-3, H-5, H-6, H-7, H-8), 4.94 (q, 1, H−, $J_{A,X}=9$ Hz, $H_{B,H}=5$ Hz), 5.3, (s, 1, OH), 7.78 (m, 6, H-B, H-1′,H-6′), 8.15-8.8 (m, 6, H-3′, H-4′, H-5′).

The other hydroxy compounds **34-39** and **41** were prepared essentially by a similar method and are listed in Table 1.

1-*α-Quinolylisopropanol* (**42**)

Ethyl quinaldate[5] (2.5 g, 0.01 mole) in dry ether (40 ml) was added dropwise to a stirred solution of CH_3MgI (0.036 mole) in dry ether (50 ml) (prepared from 0.09 g of Mg and 2.4 ml of CH_3I). The reaction mixture was refluxed for 4 hr, kept overnight and treated with 5% aq NaOH. The ether layer was separated, dried (Na_2SO_4) and evaporated to give **42**, which was purified by chromatography on a silica gel column using hexane-benzene as eluent, yield 1.9 g (64%), m.p. 65° (lit.[5] m.p. 65°); IR(KBr): 2972, 1600, 1375, 750, PMR($CDCl_3$): 1.64-2.7 (m, 6, ArH), 4.78 (s, 1, OH), 8.4 [s, 6, $(CH_3)_2$].

2-*Isopropenylquinoline* (**43**)

To a solution of **42** (1.87 g, 0.01 mole) in pyridine (50 ml) was added $SOCl_2$ (1.87g, 0.02 mole) and the reaction mixture refluxed for 3 hr. Pyridine was removed under vacuum and the residue made alkaline with aq NaOH and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to give **43** as an oil, distilled under vacuum, b.p. 124-26°/1 mm Hg, yield 0.68 g (40%); IR(neat): 3040, 3000, 1603,,770; PMR (CCl_4): 1.8-3.0 (m, 0, Ar-H), 4.45 (d, 2, CH_2), 7.77 (s, 3, CH_3).

1-*Phenyl*-4-[*β*-(2-*quinolyl*)*ethyl-β-methyl*]*piperazine* (**44**)

A mixture of N-phenylpiperazine (1.78 g, 0.011 mole), **43** (1.6 g, 0.01 mole) and acetic acid (0.6 g, 0.01 mole) in ethanol (50 ml) was refluxed for 16 hr and evaporated to dryness. The residue was made alkaline with aq NaOH and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to dryness and the residue purified by chromatography on a silica gel column using benzene with increasing proportions of ethyl acetate as eluents to give **44**, yield 50%; IR(Neat): 3370, 2928, 1600, 745; PMR ($CDCl_3$): 2.64-4.34 (m, 11, H-3, H-9, H-5, H-7, H-8, C_6H_5), 8.47 (s, 3, CH_3), 8.69 (d, 1, H-α, J = 6 Hz).

Similarly 4-*m*-tolylpiperazine was condensed with **43** to give **45**.

1-*Phenyl*-4-[*β*-4-*quinolyl*]*ethyl piperazine* (**47**)

A mixture of 4-methylquinoline[5] (1.43 g, 0.01 mole), N-phenylpiperazine hydrochloride (1.98 g, 0.01 mole) and formaldehyde (0.3 ml) was heated at 100° for 2 hr, cooled and made alkaline with aq NaOH. The separated oil was extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated to give **47**, which was purified by chromatography on basic alumina column using benzene as eluent, yield 1.95 g (65%); IR(neat): 2965, 1600, 745, 685; PMR ($CDCl_3$): 2.07-4.17 (m, 11, Ar-H), 5.3-8.2 (m, 12, aliphatic H). Similarly other compounds **48-51** were prepared and are described in Table 1.

1-*Phenyl*-4-(*β*-1-*isoquinolyl*)*ethylpiperazine* (**53**)

A mixture of 1-methylisoquinoline (**52**) (2.3 g, 0.02 mole), N-phenylpiperazine hydrochloride (1.98 g, 0.01 mole) and formaldehyde (0.8 ml) was heated at 100° for 2 hr. The reaction mixture was worked up as described for **47** and the crude **53**. Thus obtained was purified by chromatography on basic alumina column using benzene with increasing proportions of ethyl acetate as eluents, yield 4.8 g (80%); IR(neat): 2965, 1600, 734, 680; PMR ($CDCl_3$): 1.17-2.34 (m, 11, Ar-H), 5.7-8.35 (m, 12, aliphatic H).

The various other compounds (**54-57**) were prepared similarly (Table 1).

QSAR methods

The octanol/water partition co-efficients of the molecules were calculated according to the 'Con-

Table 4—Physicochemical properties and activities of 2-substituted quinoline analogues

Compd	Log P	Log (BP fall)		Total sigma[a]	Total resonance	Total polar	Total MR
		Obs.	Cal.				
3	2.04	1.15	—	—	—	—	—
7	3.86	1.72	1.73	0.0	0.0	0.0	3.09
8	5.18	1.20	1.26	−0.34	−0.26	−0.08	12.33
9	4.74	1.68	1.64	0.43	0.19	0.38	7.08
10	5.28	1.11	1.14	0.60	−0.30	0.82	13.09
13	4.00	1.84	1.78	0.06	−0.34	0.43	2.98
14	4.00	1.78	1.78	0.80	−0.34	0.43	2.98
15	5.18	1.20	1.26	−0.17	−0.13	−0.04	7.71
16	4.19	1.90	1.80	−0.27	−0.51	0.26	9.93
17	4.52	1.89	1.74	−0.07	−0.13	−0.04	7.71
18	4.57	1.73	1.72	0.23	−0.15	0.41	8.09
19	4.57	1.76	1.72	0.37	−0.15	0.41	8.09
20	3.59	1.48	1.58	—	—	—	—
22	2.36	1.38	—	—	—	—	—
25	3.79	1.60	1.70	0.0	0.0	0.0	3.09
26	4.45	1.78	1.76	−0.07	−0.13	−0.04	7.71
27	4.45	1.81	1.76	−0.17	−0.13	−0.04	7.71
34	3.36	1.48	1.39	0.0	0.0	0.0	3.09
36	3.27	1.48	1.32	−0.27	−0.51	0.26	9.93
37	3.50	1.50	1.52	0.06	−0.34	0.43	2.98
38	4.02	1.60	1.78	−0.17	−0.13	−0.04	7.71
40	3.05	1.00	1.04	—	—	—	—
41	4.02	1.70	1.78	−0.07	−0.13	−0.04	7.71
44	4.27	1.70	1.80	0.0	0.0	0.0	3.09
45	4.93	1.60	1.50	−0.07	−0.13	−0.04	7.71

(a) Total of *ortho*, *meta* and *para* substituents on the phenyl ring substituted on the piperazine portion.

structionist' approach of Hansch and Leo[13]; Sigma, Resonance, polar and MR values have been taken from the literature[13] (Table 4) and computed for the substituents present on *ortho*, *meta* and *para* positions of phenyl ring of 4-arylpiperazine derivatives. A multiple regression anàlysis programme of Labsware software was applied for deriving the correlations on IBM PC XT computer.

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Antiparasitic agents: Part VIII† – Synthesis of 1,6- and 1,8-disubstituted-9*H*-pyrido[3,4-*b*]indoles and 2-substituted-1(3),10-dihydro-9-phenylpyrido-[3,4-*b*]imidazo[4,5-*g*]indoles and their anthelmintic activity‡

Alka Agarwal, Shiv K Agarwal & D S Bhakuni*
Division of Medicinal Chemistry
and
Suman Gupta & J C Katiyar
Division of Parasitology, Central Drug Research Institute, Lucknow 226 001

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1,6-Disubstituted-9*H*-pyrido[3,4-*b*]indoles (**6-17**), 1-phenyl-8-substituted-9*H*-pyrido[3,4-*b*]indoles (**18-23**), and 2-substituted-1(3),10-dihydro-9-phenylpyrido[3,4-*b*]imidazo[4,5-*g*]indoles (**28**, **29**) have been synthesized and evaluated for their anthelmintic activity against *Ancylostoma ceylanicum*, *Nippostrongylus brasiliensis* and *Hymenolepis nana*. Compounds **11** and **22** show 100 per cent activity against *A. ceylanicum* and *H. nana* infection respectively at 250 mg/kg dose. The remaining compounds either exhibit low activity or are inactive. Some of these compounds have also been evaluated for CNS and CVS activities. However, none of these show promising activities.

Antiparasitic activity of the carboline alkaloids reported recently[2,3] and the established effectiveness of benzimidazole pharmacophore[4,5] in parasitic chemotherapy prompted us to undertake the synthesis of 2-substituted-1(3),10-dihydro-9-phenylpyrido[3,4-*b*]imidazo[4,5-g]indoles, 1,6-disubstituted-9*H*-pyrido[3,4-*b*]indoles and 1,8-disubstituted-9*H*-pyrido[3,4-*b*]indoles. In the present paper, we report the synthesis and anthelmintic activity of 1,6-disubstituted-9*H*-pyrido[3,4-*b*]indoles (**6-17**), 1-phenyl-8-substituted-9*H*-pyrido[3,4-*b*]indoles (**18-23**), and 2-substituted-1(3),10-dihydro-9-phenylpyrido-[3,4-*b*]imidazo[4,5-*g*]indole (**28,29**).

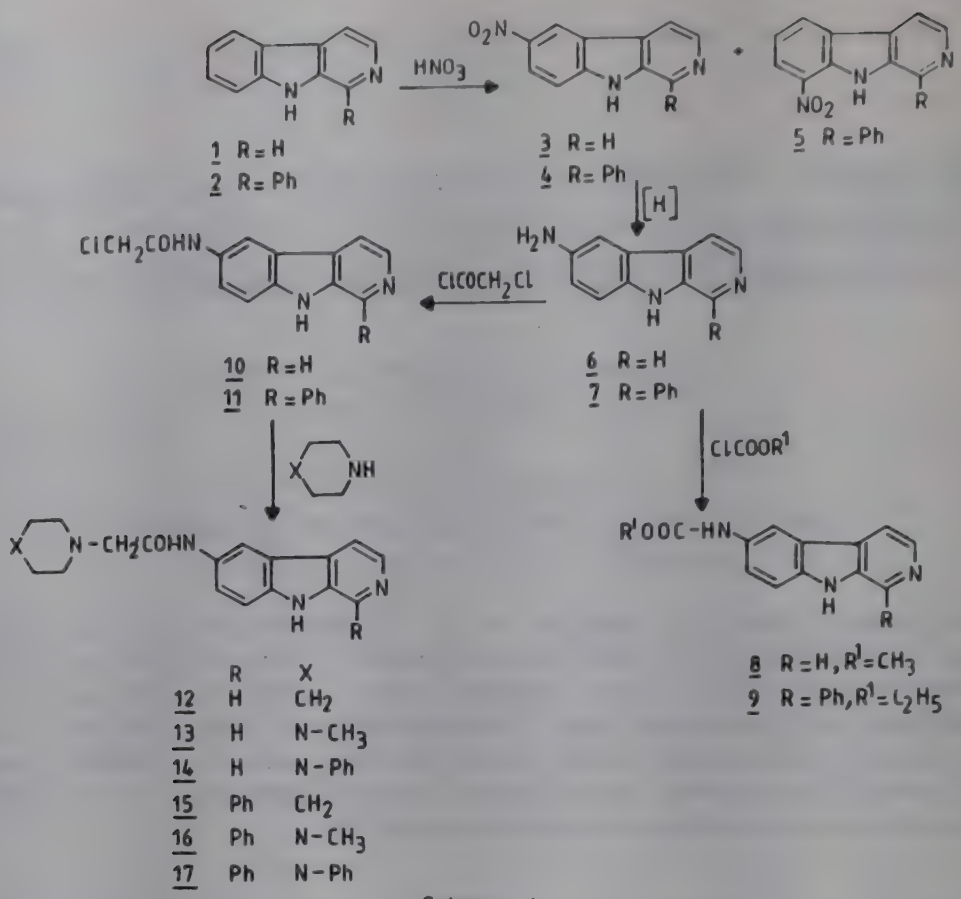
Nitration of 1-substituted-9*H*-pyrido[3,4-*b*]indoles (**1**, **2**) (Scheme 1) gave two compounds, 6-nitro-1-substituted-9*H*-pyrido[3,4-*b*]indoles (**3,4**; 64%) and 1-phenyl-8-nitro-9*H*-pyrido[3,4-*b*]indole (**5**; 35%). Reduction of **3-5** with Raney nickel afforded the corresponding 6-/8-amino-1-substituted-9*H*-pyrido[3,4-*b*]indoles (**6,7,18**; Schemes 1 and 2), which on treatment with alkyl chloroformate afforded the respective carbamates (**8,9** and **19**). Treatment of **6**, **7** and **18** separately with chloroacetyl chloride yielded the chloro acetamido derivatives **10**, **11** and **20** respectively. Condensation of **10**, **11** and **20** separately with piperidine and piperazines afforded the piperidinyl and piperizinyl acetamido derivatives (**12-17** and **21-23**) respectively (Table 1).

Acetylation of 8-amino-1-phenyl-9*H*-pyrido[3,4-*b*]indole (**18**; Scheme 3) gave 8-acetamido-1-phenyl-9*H*-pyrido[3,4-*b*]indole (**24**; 100%). Nitration of **24** afforded 8-acetamido-7-nitro-1-phenyl-9*H*-pyrido[3,4-*b*]indole (**25**; 87%). Treatment of **25** with ethanolic sodium hydroxide yielded **26** (98%) which on reduction with Raney nickel followed by cyclisation with 1,3-dicarbome-

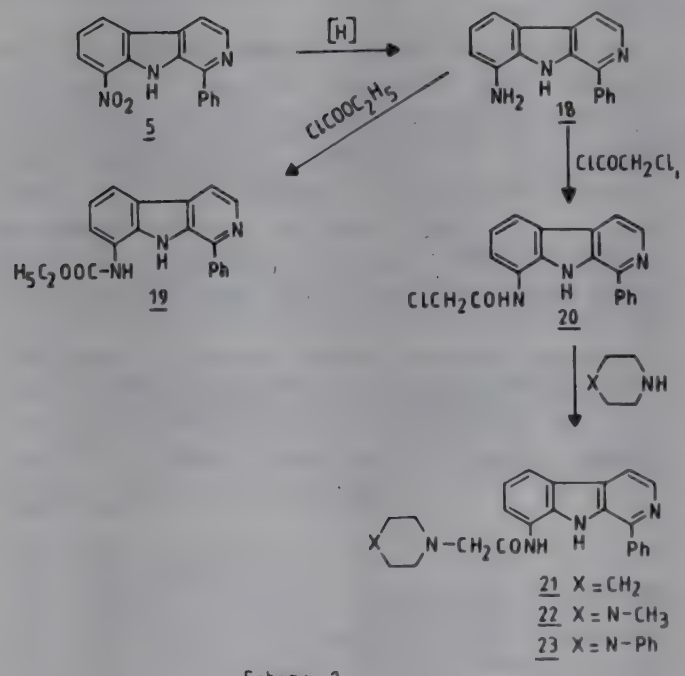
Table 1 – Physical constants and elemental analyses of 1,6-/1,8-disubstituted-9*H*-pyrido[3,4-b]indoles

Compd	m.p. °C	Yield (%)	Mol. formula	N (%)	
				Found	Calc.
8	260	56	$C_{13}H_{11}N_3O_2$	17.4	17.4
10	> 360	85	$C_{13}H_{10}N_3OCl$	15.8	16.2
12	220	67	$C_{18}H_{20}N_4O$	18.2	18.2
13	> 300	40	$C_{18}H_{21}N_5O$	21.4	21.7
14	230	67	$C_{23}H_{23}N_5O$	18.1	18.2
15	140	66	$C_{24}H_{24}N_4O$	14.4	14.6
16	264	57	$C_{24}H_{25}N_5O$	17.2	17.5
18	120	69	$C_{17}H_{13}N_3$	16.1	16.2
19	210-14	71	$C_{20}H_{17}N_3O_2$	12.6	12.7
20	> 360	98	$C_{19}H_{14}N_3OCl$	12.4	12.5
21	225	82	$C_{24}H_{24}N_4O$	14.3	14.6
22	189	91	$C_{24}H_{25}N_5O$	17.4	17.5
23	140	69	$C_{29}H_{27}N_5O$	15.1	15.2

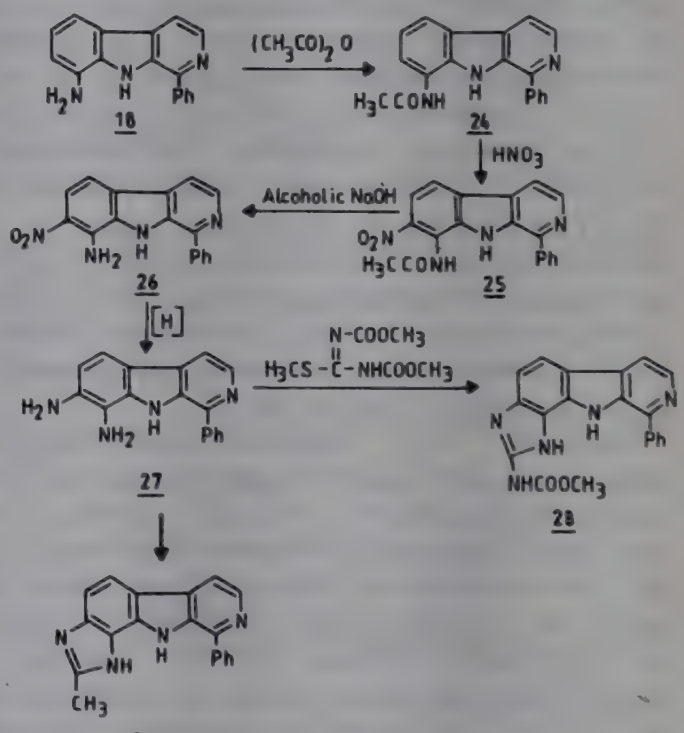
† For Part VII of the series, see ref. 1.
‡ CDRI Communication No. 4335.



Scheme 1



Scheme 2



Scheme 3

thoxy-S-methylisothiourea afforded 1(3),10-dihydro-9-phenylpyrido [3,4-*b*] imidazo [4,5-*g*] indole-2-carbamate (**28**; 50%), while cyclisation of **26** with CH_3COOH furnished 1(3),10-dihydro-2-methyl-9-phenylpyrido[3,4-*b*]imidazo[4,5-*g*]indole (**29**).

Antihelminthic activity

The compounds were evaluated against experimental infection of *A. ceylanicum* in hamsters, *N. brasiliensis* in rats and *H. nana* in rats and mice. Mebendazole was used as a standard drug which killed 100% of *A. ceylanicum* at an oral dose of 1 mg/kg × 3 and 72% worms were cleared up in *N. brasiliensis* infection at an oral dose of 100 mg/

kg × 3. The worms were not cleared up in *H. nana* infection at an oral dose of 400 mg/kg × 3.

Antihelminthic activity of the compounds **4-29** are summarized in Table 2. The compounds evaluated have been classified on the basis of their substitution pattern (series A-E).

1-Phenyl-6-substituted-9*H*-pyrido [3,4-*b*] indole (**11**) of series-A, caused 100% elimination of worms in hamsters infected with *A. ceylanicum* at an oral dose of 250 mg/kg and 50% reduction of worms at 100 mg/kg. However, it exhibited 50% activity against *N. brasiliensis* and found completely inactive against *H. nana*. Substitution of nitro group at C-6 (compound **4**) caused 20% reduction of worms of both *A. ceylanicum* and *N. brasiliensis*. Replacement of nitro group with amino function at C-6 (compound **7**) reduced the activity against *A. ceylanicum* considerably whereas the activity against *N. brasiliensis* marginally increased. The remaining compounds in the series either exhibited low order of activity or were found inactive at a dose of 250 mg/kg. None of these compounds exhibited any activity at this dose against *H. nana*.

In series-B, the compounds **8** and **10** caused 100% removal of the proglottids of *H. nana*. However, complete clearance of proglottids of the worms alongwith their scolices was not achieved.

Table 2 – Antihelminthic and antiamoebic activities of substituted 9*H*-pyrido[3,4-*b*]indoles (Series A-E)

Compd	Substituent	Position	*A. ceylanicum*[a]	*N. brasiliensis*[c]	*H. nana*[d]	*E.histolytica* (μg/ml)
		Series-A				
4	NO_2	C-6	20	20	0	–
7	NH_2	C-6	8	30	0	–
9	$NHCOOC_2H_5$	C-6	31	31	0	250
11	$NHCOCH_2Cl$	C-6	100; 50[b]	50	0	125
15	Piperidino-CH_2CONH–	C-6	20	0	0	–
16	4-Methyl-1-piperazinyl-CH_2CONH–	C-6	0	12	0	–
17	4-Phenyl-1-piperazinyl-CH_2CONH–	C-6	16	0	0	–
		Series-B				
8	$NHCOOCH_3$	C-6	0	0	100[e]	62.5
10	$NHCOCH_2Cl$	C-6	0	17	100[e]	–
14	4-Phenyl-1-piperazinyl-CH_2CONH–	C-6	62	0	0	125
		Series-C				
18	NH_2	C-8	0	63	0	250
19	$NHCOOC_2H_5$	C-8	40	60	0	–
20	$NHCOCH_2Cl$	C-8	8	40	0	–
21	Piperidino-CH_2CONH–	C-8	62	0	0	–
22	4-Methyl-1-piperazinyl-CH_2CONH–	C-8	0	0	100	–
23	4-Phenyl-1-piperazinyl-CH_2CONH–	C-8	16	13	0	–
24	$NHCOCH_3$	C-8	40	24	0	125
		Series-D				
25	$NHCOCH_3$	C-8	0	29	0	–
26	NH_2	C-8	16	20	0	–
		Series-E				
28	$NHCOOCH_3$	C-2	65	0	0	–
29	CH_3	C-2	27	32	0	–

[a] *A. ceylanicum* at 250 mg/kg × 1.
[b] *A. ceylanicum* at 100 mg/kg × 1.
[c] *N. brasiliensis* at 250 mg/kg × 3.
[d] *H. nana* at 250 mg/kg × 3.
[e] Did not clear proglottids completely along with their scolices.

Compound **8** was found completely inactive against *A. ceylanicum* and *N. brasiliensis*. Compound **10** exhibited low order of activity against *N. brasiliensis* and was found completely inactive against *A. ceylanicum*. Compound **14** exhibited 62% activity against *A. ceylanicum*. However, it was found completely inactive against *N. brasiliensis* and *H. nana*.

Compound **22** in series-C, completely eliminated (100%) the worms of *H. nana* with their scolices. However, **22** was found completely inactive against *A. ceylanicum* and *N. brasiliensis* infection. Compounds **21** showed 62% activity against *A. ceylanicum* infection and compounds **18** and **19** showed above 60% activity against *N. brasiliensis*. None of the compounds in series-D exhibited any promising activity. Compound **28** and **29** in series-E showed 65% and 31% worm reduction of *A. ceylanicum* infection respectively, whereas compound **29** also exhibited 32% activity against *N. brasiliensis*.

Pharmacological activity

Six compounds were screened for CNS and CVS activities. The screening results are recorded in Table 3. All the compounds in general exhibited depressant action that implies reduced spontaneous motor activity, sedation, hypothermia ataxia and loss of wrighting reflux. None of the compounds, however, showed any promising activity.

Antiamoebic activity

Compounds **8**, **9**, **11**, **14**, **18** and **24** were tested *in vitro* for their antiamoebic activity against *E. histolytica* (NIH-200)[6] strain in axenic culture. Compounds **9** and **18** exhibited activity at 250 μg/ml activity and compounds **11**, **14** and **24** showed activity at 125 μg/ml, whereas **8** was found active at 62.5 μg/ml, and at lower doses these compounds were found inactive.

Metronidazole was run as a control drug and was active at 8 μg/ml.

Experimental Procedure

The compounds were routinely checked for their purity by TLC on SiO_2 gel or Al_2O_3 plates. IR spectra were recorded in KBr on a Perkin-Elmer infracord (ν_{max} in cm^{-1}), PMR spectra on a Varian EM-360L (California, USA) (60 MHz) or Perkin-Elmer R-32 (90 MHz) spectrometer using TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on a Jeol-JMS D-300 spectrometer. Melting points were determined in an electrically heated apparatus and are uncorrected.

Table 3 – Pharmacological activities data of substituted 9*H*-pyrido[3,4-*b*]indoles

Compd	CVS activities[a]	Other activities
4	−24(9)	0
5	−40(150)	NM[b] 20
7	0	AI[c] 18
11	−50(11)(5)	0
24	−22(Tr)	AI 15
25	−22(6)(5)	0

[a]Fall in blood pressure in mm Hg at 1 mg/kg i.v. unless otherwise indicated in parenthesis after duration in minutes.
[b]NM = Nictitating membrane block (cat) at 1 mg/kg (i.v.).
[c]AI = Antiinflammatory at 30 mg/kg against carageenan induced oedema in rat.

6-Nitro-1-phenyl-9H-pyrido[3,4-b]indole (**4**) *and 8-nitro-1-phenyl-9H-pyrido[3,4-b]indole* (**5**)

Compounds **4** and **5** were prepared by modification of the reported method[7]. 1-Phenyl-9*H*-pyrido[3,4-*b*]indole (10 g, 41 mmole) was added in small portions to a stirred ice cooled conc. HNO_3 (20 ml) over a period of 30 min. Gl. acetic acid (150 ml) was then added to it and the mixture refluxed for 8 hr and cooled. The solid, thus separated, was filtered and washed with gl. acetic acid (25 ml). The product obtained was suspended in water (200 ml), basified with NH_4OH solution, filtered and crystallised from ethanol to give **4**, yield 7.55 g (64%), m.p. 280° (lit.[7] 232-3°); IR: 3400, 3100, 1620, 1520, 830, 740, 690; PMR(DMSO-d_6): 9.56 (d, 1H, H-5, $J_{5,7}$ = 2 Hz), 8.91 (d, 1H, H-3, $J_{3,4}$ = 6 Hz), 8.72 (d, 1H, H-4, $J_{3,4}$ = 6 Hz),8.52 (dd, 1H, H-7, $J_{5,7}$ = 2 Hz, $J_{7,8}$ = 8 Hz), 8.0 (dd, 2H, *o*-proton of phenyl group, J = 7 Hz, J = 3 Hz), 7.84 (d, 1H, H-8, $J_{7,8}$ = 8 Hz), 7.8-7.73 (m, 3H, ArH); MS: m/z 289 (M^+) (Found: N, 14.3. $C_{17}H_{11}N_3O_2$ requires N, 14.5%).

The acidic filtrate was concentrated *in vacuo* to dryness. The residue was suspended in water (100 ml) and neutralized with NH_4OH solution. The precipitate, thus obtained, was filtered, washed with water and crystallised from ethyl acetate to afford **5**, yield 4.15 g (35%), m.p. 216-20° (lit.[7] 230-1°); IR: 3330, 3040, 1620, 1560, 820, 740, 700; PMR($CDCl_3$): 10.15 (bs, 1H, indole NH), 8.55 (d, 1H, H-3, $J_{3,4}$ = 6 Hz), 8.35 (dd, 1H, H-7, $J_{6,7}$ = 8 Hz, $J_{5,7}$ = 2 Hz), 7.52 (d, 1H, H-4, $J_{3,4}$ = 6 Hz), 8.0-7.4 (m, 5H, ArH), 7.28 (t, 1H, H-6, J = 8 Hz); MS: m/z 289 (M^+) (Found: N, 14.4. $C_{17}H_{11}N_3O_2$ requires N, 14.5%).

6-Amino-1-phenyl-9H-pyrido[3,4-b]indole (**7**)

A mixture of **4** (7 g, 24.2 mmole), Raney nickel (2.3 g) and ethanol (80 ml) under a pressure of H_2

in a parr apparatus at 2.5 kg/cm^2 was shaken for 8 hr. The resulting mixture was warmed and the catalyst filtered off. The filtrate was concentrated *in vacuo* to give the crude product, which was crystallized from ethanol to give **7**, yield 5.15 g (82%), m.p. 230-34°, IR: 3600-3300, 3100, 1600, 830, 760; PMR($CDCl_3$ + DMSO-d_6): 10.65 (bs, 1H, indole NH), 8.24 (d, 1H, H-3, $J_{3,4}$ = 5 Hz), 7.9 (dd, 1H, H-7, $J_{5,7}$ = 3 Hz and $J_{7,8}$ = 9 Hz), 7.85 (d, 1H, H-5, $J_{5,7}$ = 3 Hz), 7.62 (d, 1H, H-4, $J_{3,4}$ = 5 Hz), 7.5-7.1 (m, 5H, ArH), 6.83 (d, 1H, H-8, $J_{7,8}$ = 9 Hz), 3.9 (bs, 2H, NH_2); MS: m/z 259 (M^+) (Found: N, 15.9. $C_{17}H_{13}N_3$ requires N, 16.2%).

Similarly, compound **18** was prepared by hydrogenation of **5** and compound **6** by literature method[8]. The spectral data of the compound were in agreement with the assigned structure.

6-Carbethoxyamino-1-phenyl-9H-pyrido[3,4-b]-indole (**9**)

Ethyl chloroformate (0.284 g, 2.62 mmole) was added dropwise to a stirred solution of **7** (0.6 g, 2.32 mmole) in ethanol (20 ml) at 0-5° and the mixture stirred at ambient temperature for 1 hr. The solvent was removed *in vacuo* and the residue neutralized with aq. Na_2CO_3 solution (10%). The solid thus separated was filtered and crystallized from methanol to give **9**, yield 0.63 g (82%), m.p. 130°; IR: 3500-3400, 3050, 2960, 1680, 820, 760, 700; PMR($CDCl_3$): 9.13 (bs, 1H, indole NH), 8.47 (d, 1H, H-3, $J_{3,4}$ = 5 Hz), 8.17 (d, 1H, H-5, $J_{5,7}$ = 2 Hz), 8.0-7.8 (dd, 2H, H-7 and H-8, $J_{5,7}$ = 2 Hz and $J_{7,8}$ = 8 Hz), 7.73 (d, 1H, H-4, $J_{3,4}$ = 5 Hz), 7.6-7.1 (m, 5H, ArH), 4.2 (q, 2H, OCH_2, J = 7 Hz), 2.63 (bs, 1H, NH), 1.23 (t, 3H, CH_3); MS: m/z 331 (M^+) (Found: N, 12.7. $C_{20}H_{17}N_3O_2$ requires N, 12.7%).

Compounds **8** and **19** were prepared from **6** and **18** respectively by condensation with alkyl chloroformate. The spectral data of these compounds were in agreement with the assigned structures.

6-Chloroacetamido-1-phenyl-9H-pyrido[3,4-b]-indole (**11**)

A solution of chloroacetyl chloride (0.65 g, 5.77 mmole) in dry acetone (5 ml) was added dropwise to a stirred solution of **7** (1 g, 4.25 mmole) in dry acetone (20 ml) at ambient temperature. Stirring was continued for 30 min, the solvent and excess of reagents were removed *in vacuo* and the product was filtered, washed with water and crystallised from ethyl acetate to afford **11**, yield 1.27 g (98%), m.p. > 360°; IR: 3510-3250, 3160, 3040-2950, 1650, 840, 740, 690; PMR($CDCl_3$ + DMSO-d_6): 10.27 (bs, 1H, indole NH), 9.23 (bs, 1H, H-5), 8.33 (d, 1H, H-3, $J_{3,4}$ = 5 Hz), 8.0-7.2 (m, 8H, H-4, H-7, H-8 and ArH), 4.1 (s, 2H, CH_2), 3.55 (bs, 1H, NH) (Found: N, 12.5. $C_{19}H_{14}N_3OCl$ requires N, 12.5%).

Similarly, compounds **10** and **20** were prepared from **6** and **18** respectively. The spectral data of these compounds were in agreement with the assigned structures.

6-[β-(4-Phenylpiperazin-1-yl)acetamido]-1-phenyl-9H-pyrido[3,4-b]indole (**17**)

A mixture of N-phenylpiperazine (0.266 g, 1.638 mmole), **11** (0.5 g, 1.49 mmole), NaI (0.11 g), Na_2CO_3 (0.22 g) and dry N,N-dimethylformamide (6 ml) was stirred at 80° for 16 hr and the resulting mixture poured into water (10 ml). The solid, thus separated, was filtered and chromatographed on SiO_2 column. Elution with $CHCl_3$ – MeOH gave a compound and which was crystallised from ethyl acetate to yield **17**, yield 0.47 g (68%), m.p. 118°; IR: 3400-3210, 3050-2800, 1650, 830, 755, 700; PMR($CDCl_3$): 9.4 (bs, 1H, indole NH), 8.5-8.32 (m, 2H, ArH), 8.05-7.8 (m, 3H, ArH), 7.64-7.35 (m, 5H, ArH), 7.3-6.7 (m, 5H, ArH), 3.4-3.1 (m, 6H, 3 × NCH_2), 2.9-2.65 (m, 4H, 2 × NCH_2), 2.45 (bs, 1H, NH); MS: m/z 461 (M^+) (Found: N, 14.9. $C_{29}H_{27}N_5O$ requires N, 15.2%).

Compounds **12-16** and **21-23** were obtained similarly from **10**, **11** and **20** by condensation with an appropriate base. The spectral data of these compounds were in agreement with the assigned structures.

8-Acetamido-1-phenyl-9H-pyrido[3,4-b]indole (**24**)

A mixture of 18 (1.5 g, 5.79 mmole) and acetic anhydride (5 ml) was heated at 100° for 1 hr. The resulting mixture was poured onto crushed ice and basified with aq. NaOH (10%). The product, thus obtained, was filtered, washed with water and crystallised from ethyl acetate to give **24**, yield 1.74 g (100%) m.p. 236°; IR: 3600-3400, 3200, 3040, 1650, 825, 745, 700; PMR($CDCl_3$ + DMSO-d_6): 10.73 (s, 1H, indole NH), 9.8 (s, 1H, NH), 8.36 (d, 1H, H-3, J = 6 Hz), 7.93 (dd, 1H, H-7, $J_{5,7}$ = 2 Hz and $J_{6,7}$ = 8 Hz), 7.8 (d, 1H, H-4, J = 6 Hz), 7.7 (d, 1H, H-5, J = 8 Hz), 7.6-7.3 (m, 5H, ArH), 7.1 (t, 1H, H-6, J = 8 Hz), 2.14 (s, 3H, $NCOCH_3$); MS: m/z 301 (M^+) (Found: N, 13.7. $C_{19}H_{15}N_3O$ requires N, 13.9%).

8-Acetamido-7-nitro-1-phenyl-9H-pyrido[3,4-b]-indole (**25**)

Compound **24** (1.0 g, 3.32 mmole) was added in small portions to a stirred ice cooled conc. HNO_3

(10 ml) during 15 min. and stirring continued for 30 min. The resulting mixture was poured onto crushed ice and basified with NH_4OH solution. The product, thus obtained, was filtered, washed with water and crystallised from ethanol to give **25**, yield 0.8 g (70%), m.p. 183°; IR: 3560-3340, 3200, 3050, 1665, 1560, 1330,1300, 830, 755, 700; PMR($CDCl_3$ + DMSO-d_6): 10.2 (s, 1H, indole NH, D_2O exchangeable), 8.37 (d, 1H, H-3, J = 6 Hz),8.3 (s, 1H, NH, D_2O exchangeable), 8.25 (d, 1H, H-6, J = 8 Hz), 8.1-7.8 (m, 3H, ArH), 7.7-7.4 (m, 4H, ArH), 2.2 (s, 3H, $NCOCH_3$); MS: m/z 346 (M^+) (Found: N, 15.8. $C_{19}H_{14}N_4O_3$ requires N, 16.2%).

8-*Amino*-7-*nitro*-1-*phenyl*-9*H*-*pyrido*[3,4-*b*]*indole* (**26**)

Aq. NaOH (0.02 g, in 5 ml H_2O) was added dropwise to a stirred solution of **25** (0.5 g, 1.445 mmole) in ethanol (10 ml). The mixture was then refluxed for 3 hr, the solvent removed *in vacuo* and water (20 ml) added to it. The product, thus obtained, was filtered, washed with water and crystallised from ethanol to give **26**, yield 0.43 g (98%), m.p. 232°; IR: 3650-3300, 3050, 1590, 1500, 1320, 1280, 840, 770, 690; PMR($CDCl_3$ + DMSO-d_6): 8.7 (bs, 1H, indole NH), 8.56 (d, 1H, H-3, J = 6 Hz), 8.47 (d, 1H, H-4, J = 6 Hz), 8.03 (d, 1H, H-6, J = 8 Hz), 7.96 (m, 2H, ArH), 7.6-7.3 (m, 3H, ArH), 6.74 (s, 2H, NH_2), 6.65 (d, 1H, ArH, J = 8 Hz) MS: m/z 304 (M^+) (Found: N, 18.6. $C_{17}H_{12}N_4O_2$ requires N, 18.4%).

7,8-*Diamino*-1-*phenyl*-9*H*-*pyrido*[3,4-*b*]*indole* (**27**)

A solution of **26** (0.5 g, 1.64 mmole) in ethanol (25 ml) was hydrogenated over Raney nickel at 3 kg/cm^2 for 6 hr. The catalyst was filtered off and the solvent evaporated under reduced pressure to give **27**, yield 0.45 g (99.8%), m.p. > 300°, which was used in the subsequent reaction without purification; IR: 3650-3300, 3050,1600, 820, 740, 690, MS: m/z 274 (M^+).

1(3),10-*Dihydro*-9-*phenylpyrido*[3,4-*b*]*imidazo*-[4,5-*g*]*indole*-2-*carbamate* (**28**)

A mixture of **27** (0.45 g, 1.64 mmole), 13-dicarbomethoxy-S-methylisothiourea (0.4 g, 1.941 mmole) and ethanol (25 ml) was refluxed for 20 hr, and the product which separated out was filtered, washed with ethanol and crystallised from pyridine-water to give **28**, yield 0.21 g (50%), m.p. > 320°; IR: 3580-3200, 3050, 1700, 1650, 820, 750, 690; PMR($CDCl_3$ + DMSO-d_6): 8.9 (bs, 1H, indole NH), 8.6-7.7 (m, 3H, ArH), 7.65-6.8 (m, 6H, ArH), 4.0-3.7 (bs, 2H, NH), 3.5 (s, 3H, OCH_3) MS: m/z 357 (M^+) (Found: N, 19.4. $C_{20}H_{15}N_5O_2$ requires N, 19.6%).

2-*Methyl*-9-*phenyl*-1(3),10-*dihydropyrido*[3,4-*b*]-*imidazo*[4,5-*g*]*indole* (**29**)

CH_3COOH (5.76 g, 96 mmole) was added to a solution of diamine **27** (0.45 g, 1.64 mmole) in 4*N* HCl (20 ml) and the mixture refluxed for 30 min. The excess of solvent and reagent were removed *in vacuo* and the residue was neutralised with NH_4OH solution. The product which separated out was filtered, washed with water and crystallised from pyridine to furnish **29**, yield 0.223 g (40%), m.p. > 300°; IR: 3560-3200, 3050, 1600, 840, 760, 700; MS: m/z 298 (M^+) (Found: N, 18.4. $C_{19}H_{14}N_4$ requires N, 18.8%).

Anthelmintic Activity

(*a*) *Antihookworm screening*

The compounds were evaluated against *A. ceylanicum* in golden hamsters as per the method described earlier[9,10]. Hamsters of either sex (50-60 g) were injected orally with 60 ± 5 infective larvae (L_3) of *A. ceylanicum*. On day 17 post inoculation (p.i.) the injection was checked by ovoscopic examination of faeces. Animals showing positive infection were used in screening in a group of 3 to 5 animals per experiment in each dose schedule.

Compounds were given as a suspension in water and Tween 80. On the 3rd day of last dose the animals were sacrificed and the therapeutic efficacy of the compounds was assessed by comparing average number of worms recovered from the treated group to that of control group. The results of screening are given in Table 2.

(*b*) *Antitrichostrongylid screening*

Compounds were evaluated by the method described earlier. Freshly weaned (35-40 g) male rates (UF strain) were infected with *N. brasiliensis* (500 L_3) subcutaneously. The therapeutic trials were initiated on day 9 p.i. and continued for 3 consecutive days. The efficiency assessment was made on per cent worm reduction as described for *A. ceylanicum*. The testing results are given in Table 2.

(*c*) *Antitapeworm screening*

The testing was carried out by the method of Gupta *et al*[12]. The University of Freiburg strain of male albino rats weighing 25-30 g were infected by feeding them 200 mature viable ova of *H. nana*. On day 17th post infection, the faeces of the

animals were examined and those showing *H. nana* eggs were used in the study. The animals were divided into 4 groups each consisting of 3 to 5 rats and were given various doses of the test compounds after being starved for 6 hr. On the 3rd day of treatment, all the treated rats were again starved for 5 to 6 hr and then sacrificed. The intestine of each animal was individually examined for worms and scolices under a dissecting microscope. Because of the wide variations in the number of adult worms produced by incubating 200 viable eggs, the criterian for assessing the activity of compounds was taken as the absolute clearance of the parasites alongwith their scolices in any animal at a particular dose. Several replicates were done and results given represent the mean values.

Pharmacological activities

Six compounds (**4**, **5**, **7**, **11**, **24** and **25**) (Table 3) were tested for gross observational effect in male mice at 10 mg/kg by standard method. Effect on blood pressure and nictitating membrane blockade was studied in anaesthetized cats by administering 1 mg/kg i.v. of the compounds. Compounds were also screened for their antiinflammatory activity at 30 mg/kg dose against carageenan induced oedema in rats.

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Notes

Anion-induced reactions of primary alcohols at C-6 of 3-alkyl-6-methyl-1,3-oxazine-2,4(3*H*)-diones : Formation of N-alkyl-3-alkoxybuten-2-amides

Harjit Singh*, Pawan Aggarwal & Subodh Kumar

Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005

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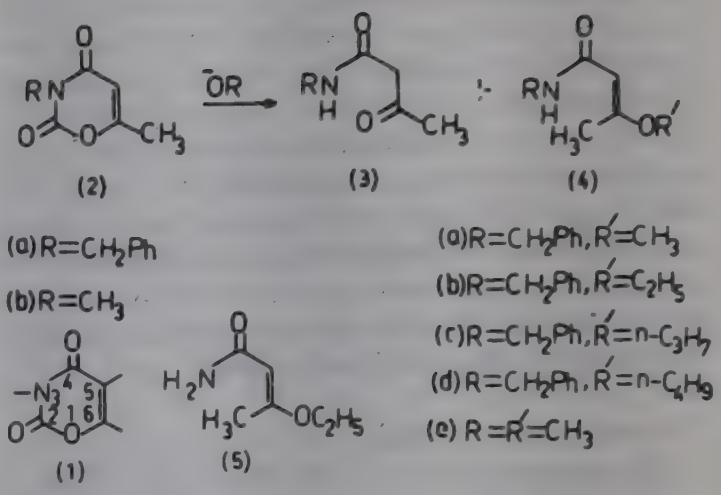
Primary alcohols react at C-6 of 3-alkyl-6-methyl-1,3-oxazine-2,4(3*H*)-diones(**2**) in the presence of Triton-B or potassium thiocyanate to give N-alkyl-3-alkoxybuten-2-amides(**4**).



Nucleophile-induced ring transformations of 1,3-oxazine-2,4(3*H*)-diones (**1**)† with hard bases (amines, alcohols) proceed by initial interaction at C-2[1–4] and those with soft bases (cyanide ion, thiols) through attack at C-6[5,6]; in the presence of a co-reagent such as Et_3N the reaction site for alcohols is changed predominantly to C-4[4]. Presently we have found that in the presence of anions such as ^-OH (benzyltrimethylammonium hydroxide, i.e. Triton-B) and ^-SCN (potassium thiocyanate), the reaction in primary alcohols exclusively occurs at C-6 of 3-alkyl-6-methyl-1,3-oxazine-2,4(3 *H*),diones (**2**).

Thus, **2a** in refluxing anhydrous methanol containing catalytic amount of Triton-B gave two products isolated by chromatography. The component with $R_f = 0.64$ (benzene : ethyl acetate :: 8:2) m.p. 40°, M^+ 205, in its ^1H NMR spectrum exhibited two 3H singlets at δ 2.3 and 3.5 due to $=\overset{|}{C}\text{-}CH_3$ and OCH_3, one 2H doublet at 4.23 and a 1H singlet at 4.90 alongwith 1H broad exchangeable signal and ArH signals. From these spectral data, this compound could be assigned the structure as N-benzyl-3-methoxybuten-2-amide (**4a**). The second component, R_f = 0.15 (benzene : ethyl acetate :: 8:2) m.p. 97°, M^+ 191, could be characterised as N-benzyl-3-oxobutanamide (**3a**)[7] by direct comparison with an authentic sample. Similarly, 3-benzyl-6-methyl-1,3-oxazine-2,4(3*H*)-dione (**2a**) with ethanol, *n*-propanol, *n*-butanol and 3,6-dimethyl-1,3-oxazine-2,4(3*H*)-dione (**2b**) with methanol gave corresponding **4** alongwith substantial amounts of **3** (Table 1)‡. ^1H NMR monitoring of these reactions showed the formation of **4** and **3** in the ratio of 9:1, which indicated that **4** underwent hydrolytic cleavage to **3** during chromatographic separation. Hence, further *in situ* use of the organic intermediates **4**, formed in good yields§ in the above manner, could be synthetically advantageous.

All these derivatives of **4** in thier IR spectra exhibited a band at 1100 cm^{-1}. In analogy with our observations, on the appearance of similar band in *E*-isomers of N-benzyl-3-alkylthiobuten-2-amides[6] and steric considerations[6,9], compounds **4** have been assigned *E*-configuration.

The effect of Triton-B in directing the reactions of alcohols at soft C-6 of **2a** and **2b** could be attributed to its equilibration with benzyltrimethylammonium alkoxide providing relatively soft ^-OR for a favourable reaction at C-6. This tendency is much more in Triton-B than in triethylamine[4] because of the formal charged character. It has also been found that the sodium ethoxide in ethanol reacts with **2a** to give **4b** (25%).

The reaction of **2a** in methanol in the presence of potassium cyanide led to **4a** (23%) and **3**(18%) and the products expected from the reaction of cyanide ion and **2a**[5] were not formed. Similarly, **2a** and methanol in the presence of potassium thiocyanate, potassium iodide, sodium azide, potassium bromide and potassium chloride gave **4a** and **2** but in lesser yields.

These results provide a methodology for the formation of 3-alkoxybuten-2-amides and are a pointer that for reaction of 1,3-oxazine-2,4(3*H*)-diones with any anion, alcohols as reaction media should be employed with caution.

†Hardness of acidic sites in **1** is in the order[5] : C-2 > C-4 > C-6.

‡However, under these reaction conditions, secondary (isopropanol and cyclohexanol) and tertiary (*t*-butanol) alcohols failed to react with **2a** and **2b** probably due to steric hindrance.

§ Only one such compound 3-ethoxybuten-2-amide **5** has earlier been obtained in only 2.6% yield[8].

Table 1—N-Benzyl 3-alkoxybuten-2-amides(**4**)*

Compd.	% yield of **4** Triton-B(KSCN)	M^+ (m/z)	^1H NMR ($\delta CDCl_3$)	% yield of **3** Triton-B (KSCN)
4a	42.0(32.0)	205	2.30(s,3H, $=-CH_3$), 3.50(s,3H,OCH_3), 4.23(d,J = 6Hz,2H,$HNCH_2$), 4.80(s,1H, $=-H$), 5.50(br,1H,NH), 7.0(s,5H,ArH)	34(32)
4b	28(−)	219	1.25(t,J = 6Hz,3H,OCH_2CH_3), 2.25(s,3H, $=-CH_3$), 3.50(q,J = 6Hz,2H,OCH_2CH_3), 4.30(d,J = 6Hz, 2H,$HNCH_2$), 4.70(s,1H, $=-H$) 7.10(s,5H,ArH)	27
4c	25(−)	233	1.25(m,5H,CH_2CH_3), 2.20(s,3H, $=-CH_3$), 3.40(t,J = 6Hz,2H,OCH_2), 4.10(d,J = 6Hz, 2H,$HNCH_2$), 4.75(s,1H, $=-H$), 7.0(s,5H,ArH)	23
4d	39(−)	247	1.25(m,7H,$CH_2CH_2CH_3$), 2.20(s,3H, $=-CH_3$), 4.10(t,J = 6Hz,2H,OCH_2), 4.30(d,J = 6Hz,2H, $HNCH_2$), 5.0(br,1H,NH), 7.20(s,5H,ArH)	9
4e	45.91(35)	129	2.20(s,3H, $=-CH_3$), 2.80(d,J = 6Hz,3H,$HNCH_3$), 3.55(s,3H,OCH_3), 4.90(s,1H, $=-H$), 5.50(b,1H,NH)	31(30)

*Except **4a**, all compounds are liquid.

Experimental

^1H NMR, IR and mass spectra were recorded on JNM PMX 60 MHz, PYE UNICAM SP3-300 and Jeol JMS-D-300 instruments respectively.

3-Alkyl-6-methyl-1,3-oxazine-2,4(3 *H*)-diones (**2a**, **2b**) were refluxed in respective alcohols containing a catalytic amount of Triton-B or potassium thiocyanate (3 equivalent). Afte the completion of reaction (TLC) which took 5 to 7 hr, the solvent was distilled off and the residue was chromatographed over silica using benzene : ethyl acetate as eluent to isolate the compounds **4** and **3**.

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Condensation of 2,2′-methylene-bis(cyclohexane-1,3-diones) with diamino-maleonitrile

K Joseph Prabahar, K Rajagopalan & V T Ramakrishnan*
Department of Organic Chemistry,
University of Madras, Guindy Campus, Madras 600 025

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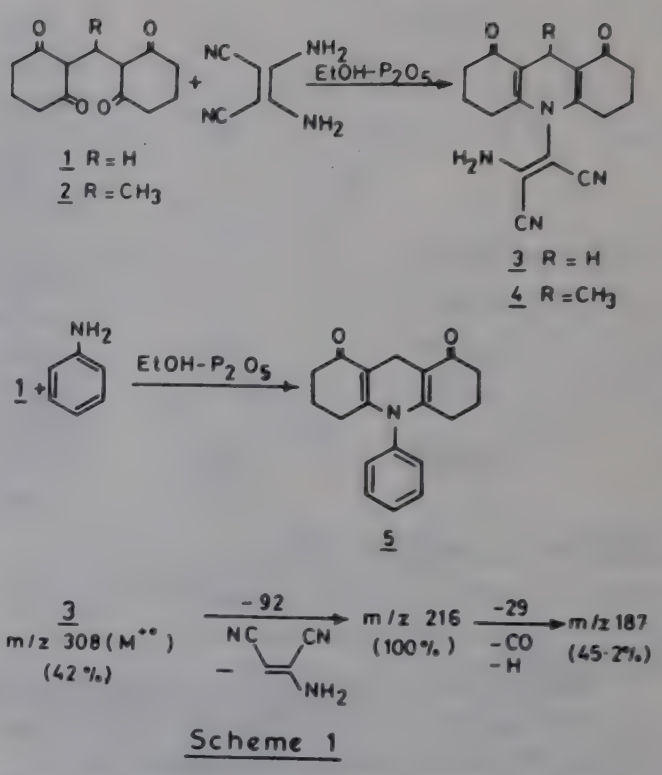
Condensation of 2,2′-methylenebis(cyclohexane-1,3-diones) (**1** and **2**) with diaminomaleonitrile gives the decahydroacridine-1,8-dione derivatives (**3** and **4**).

Both diiminosuccinonitrile (DISN)[1,2] and diaminomaleonitrile (DAMN)[3-5] have received considerable attention in terms of their potentials for the synthesis of a variety of heterocyclic compounds. In our efforts to utilize DAMN for the synthesis of novel heterocyclic systems, its condensation with 2,2′-methylene-bis(cyclohexane-1,3-dione) (**1**)[6] was attempted. Reacting one equivalents each of DAMN and **1** in ethanol, in the presence of a catalytic amount of P_2O_5 at room temperature followed by usual work up of the reaction mixture furnished a high melting crystalline solid (**3**) (decomposed above 220°) in 55% yield. The homologue **2** of **1** behaved in a similar manner towards DAMN giving a crystalline solid (**4**) in 55% yield, which decomposed above 200°. The PMR of **3** in DMSO-d_6 was not very informative; it merely showed a broad multiplet between δ 1.9-2.8 (12H), a singlet at 3.1 (2H, CH_2) and a broad singlet at 8.5. The high resolution GC-mass spectrum showed it to be a homogeneous compound with a molecular weight 308. Based on these data, structure **3** was assigned to the compound.

The mass spectral fragmentation (Scheme 1) supported the assigned structure.

Confirmatory evidence for the structure was obtained by a single crystal X-ray crystallographic study of the compound **4**. The crystal belongs to the space group PI with the cell constants: a = 8.5138 (6), b = 9.407 (3), c = 11.8388 (14) A°, α = 70.76 (2), β = 79.4855 (8) and γ = 79.50 (2).

Our attempts to effect aromatization of the end rings of compound **3** were not successful. A model reaction involving aniline and compound **1** gave the N-phenylacridine derivative (**5**) in 60% yield [m.p. 260°(d)].



Scheme 1

To our knowledge the formation of an acridine derivative using DAMN has not been reported so far.

Acknowledgement

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Enamines: Part VI – A new synthesis of ibuprofen †

Sheshgiri N Kulkarni, N K Bhamare & H Vasanti Kamath*
National Chemical Laboratory, Pune 411 008

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Morpholine enamine of 4-methylpentaldehyde (4) on reaction with methyl vinyl ketone followed by hydrolysis gives an isomeric mixture of 4-isobutylcyclohexenones. This isomeric mixture on Reformatsky reaction with 2-bromopropionic ester followed by aromatisation and hydrolysis gives ibuprofen.

2-(4-Isobutylphenyl)propionic acid, which is a non-steroidal anti-inflammatory drug, is extensively used in clinical practice and is marketed under the trade name Ibuprofen. The various approaches towards the synthesis of this compound are described in a recent review[1]. Our interest in enamine chemistry, prompted us to develop a method (see Chart 1) which involves enamine and aromatisation of substituted cyclohexane system. There are three methods[2-4] which involve either enamines or aromatisation step.

Magnesium isoamylbromide (**1**) was condensed with dimethylformamide to afford a sticky magnesium complex (**2**) which was stirred at room temperature for 72 hr. The IR spectrum of the supernatent solution of the reaction mixture showed a weak band at 1640 cm^{-1} characteristic of enamine. Work-up of the reaction mixture gave enamine (**3**) in 25% yield. Since the yield of the enamine was only 25%, the whole reaction mixture was treated with 3*N* HCl to obtain 4-methylpentaldehyde[5] (**4**). The aldehyde (**4**) was converted to its morpholine enamine (**5**) by standard method and subsequently was condensed with methyl vinyl ketone in dry ether Chart 1. Usual work-up gave a mixture of 4-isobutylcyclohex-2-en-1-one (**6**) and 4-isobutylcyclohex-3-en-1-one (**7**) as 70:30 mixture as shown by GLC analysis. The mixture of **6** and **7** was subjected to Reformatsky reaction using zinc and ethyl 2-bromopropionate to give a mixture of hydroxy compounds **8** and **9** which was aromatised with *p*-toluenesulphonic acid in refluxing toluene to obtain ester (**10**) of 2-(4-isobutylphenyl)propionic acid. The ester (**10**) on hydrolysis with 30% sodium hydroxide solution gave the title compound in 90% yield; m.p. 76°C (ref. 6), agreeing in all respects with authentic sample.

Experimental

Melting points are uncorrected. PMR spectra were recorded on a Varian T-60 spectrometer with TMS as an internal standard and IR spectra of liquids recorded as smears and solids as nujol mulls on Perkin-Elmer model 683 spectrophotometer and ν_{max} given in cm^{-1}. GLC was run on Hewlett-Packard 5730 A instrument with OV-101 column at 160°C. Mass spectra were recorded on a CEC-2-110B double focussing spectrometer using direct inlet system at 70 eV.

1-N,N-Dimethylamino-4-methyl-pent-1-ene (**3**)

Magnesium (5.4 g, 0.22 mole) was added to dry ether (50 ml) under stirring, to which a crystal of iodine was added to initiate the reaction. Isoamylbromide (30.2 g, 0.2 mole) in dry ether (20 ml) was then added dropwise and the reaction mixture refluxed for 3 hr until the magnesium dissolved. Additional ether (100 ml) was added at this state and the contents were cooled in an ice-salt bath. N,N-Dimethylformamide (17.52 g, 0.24 mole) was then added slowly over 45 min. The reaction mixture was further stirred for 72 hr; filtered and the filtrate was concentrated and distilled at 82-85°C/90 mm to give **3**, yield 6.35 g (25%); IR: 1640 ($-CH=CH-N\langle$; PMR (CCl_4): δ 0.9 [d, 6H, $-CH(CH_3)_2$, J = 6 Hz], 1.85 (m, 2H, allylic CH_2), 2.5 (s, 6H, $-N(CH_3)_2$, 4.05 (m, 1H, J = 14 Hz, $HC=CH-N\langle$), 5.7 (d, 1H, J = 14 Hz, $HC=CH-N\langle$).

4-Methylpentaldehyde (**4**) *and* *1-Morpholino-4-methyl-pent-1-ene* (**5**)

The Grignard complex was prepared as given above and decomposed with 3*N* HCl, organic layer separated, washed with 5% sodium bicarbonate solution, dried, concentrated and distilled at 115-20°C at atmospheric pressure to get **4** in 79% yield (18.3 g); IR: 2700 ($-\overset{O}{\overset{\|}{C}}-H$); 1722 ($-\overset{O}{\overset{\|}{C}}-O$); PMR ($CCl_4$): δ 0.9 [d, 6H, $-CH-(CH_3)_2$], 1.5 (m, 2H, $-CH_2$), 2.2 (m, 2H, CH_2CO), 3.4 [m, 1H, $CH(CH_3)_2$], 9.7 (1H, $-C-H$).

The morpholine-enamine (**5**) was prepared by the addition of morpholine (24.36 g, 0.28 mole) dropwise to a stirred ice-cooled solution of **4**

† NCL Communication No. 4634.

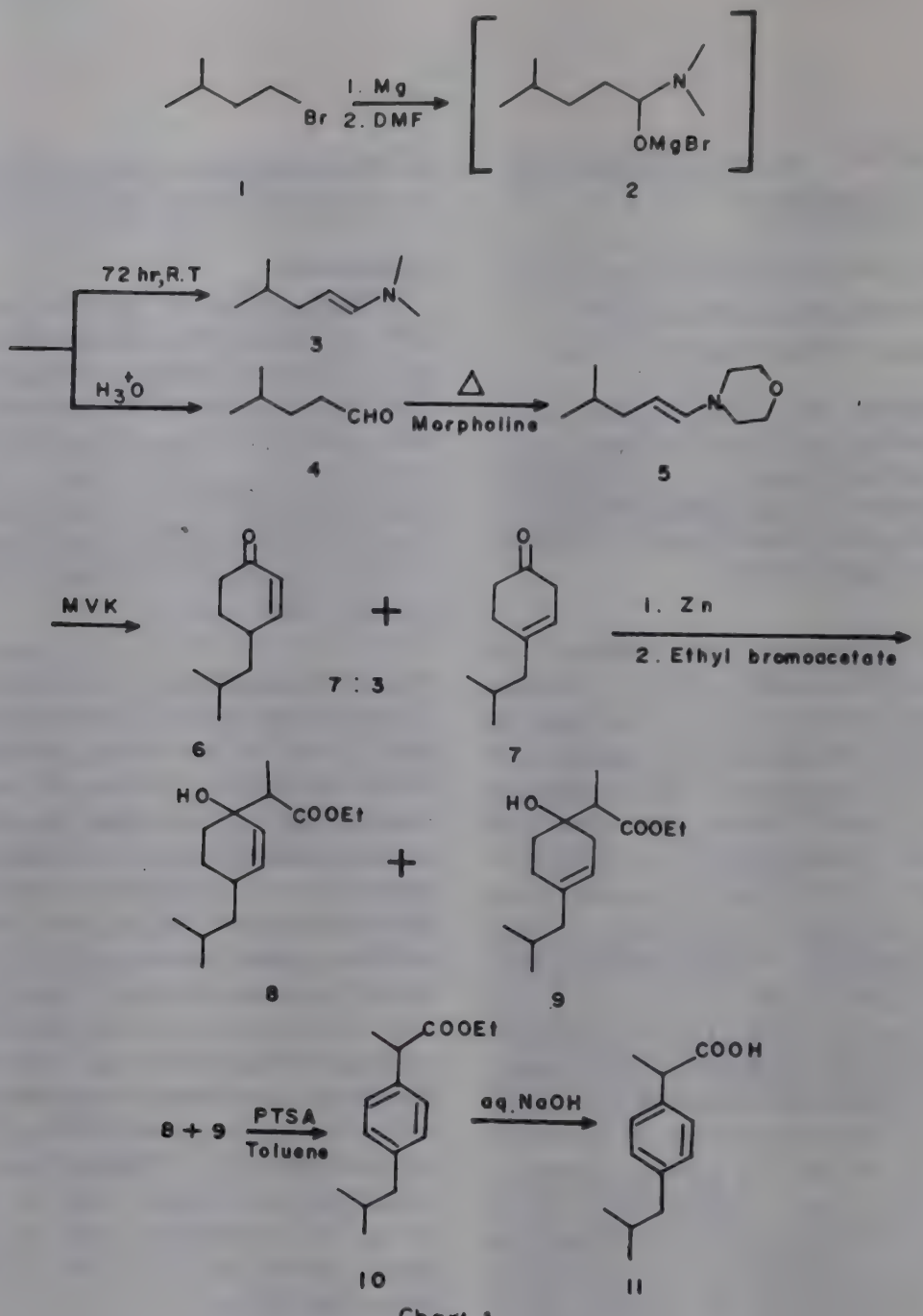

Chart 1

(14.0 g, 0.14 mole) and anhydrous potassium carbonate (7.8 g) and the mxiture stirred at room temperature for 8 hr. Potassium carbonate was removed by filtration and the residue distilled at 67-70°/20 mm to yield **5** (15.47 g, 65%); IR: 1650 ($-CH=CH-N$); PMR(CCl_4): δ 0.9 [d, 6H, J = 6 Hz, $CH(CH_3)_2$], 1.85 (m, 2H, $CH_2-CH=CH-$), 2.3 [m, 1H, $-CH-(CH_3)_2$], 2.7 [t, 4H, $-N-(CH_2)_2$], 3.6 [t, 4H, $O(CH_2)_2$], 4.2 (m, 1H, J = 14 Hz, $-CH=CH-N$, 5.6 (d, 1H, J = 14 Hz, $-CH=CH-N$

4-Isobutylcyclohex-2-en-1-one (**6**) *and 4-isobutylcyclohex-3-en-1-one* (**7**)

To a stirred ice-cooled solution of **5** (15.21 g, 0.09 mole) in dry ether (50 ml) was added dropwise, under nitrogen atmosphere, methyl vinyl ketone (6.7 g, 0.09 mole) over 30 min. After stirring for 22 hr at room temperature, the mixture was decomposed by the addition of 15% HCl (190 ml) and the mixture was further stirred for 30 hr. The organic phase was separated, washed with dil. HCl, water, dried over sodium sulphate and the solvent evaporated. The residue distilled at 140°/120 mm. Yield of (**6**) + (**7**) was 12.47 g (90%); IR: 1685 ($\geq C=O$-α,β-isomer) 1715 ($\geq CO-$β,γ-isomer); PMR (CCl_4): δ 8.10 [d, 6H, J = 6.5 Hz, $-CH-(CH_3)_2$], 5.45 (t, 1H, $-\overset{O}{\overset{\|}{C}}-CH_2-CH=$

CH− in **7**), 5.85 (d, 1H, J = 12 Hz, $-\overset{\overset{O}{\|}}{C}-CH=$ CH− in **6**), 6.8 (d, 1H, J = 12 Hz, $-\overset{\overset{O}{\|}}{C}-CH=$ C*H*− in **6**). GLC showed 70:30 mixture of **6** and **7**.

4-*Isobutyl*-1-(2-*ethyl propionate*)*cyclohex*-2-*en*-1-*ol* (**8**) *and* 4-*isobutyl*-1-(2-*ethylpropionate*)*cyclohex*-3-*en*-1-*ol* (**9**)

To zinc dust (previously dried at 100°C, 4 g, 0.061 mole) was added a solution of ethylbromoacetate (8.35 g, 0.05 mole) and mixture of **6** and **7** (9.12 g, 0.06 mole) in dry benzene (8 ml) and dry ether (2 ml) through a dropping funnel. The addition was such that, initially only 1 ml was added and the flask was warmed gently till the reaction commenced and the remaining mixture was added when moderate refluxing started. It was then further stirred for 30 min, cooled in an ice-bath and sulphuric acid (10%, 20 ml) was added under vigorous stirring. The organic phase was separated and washed with 5% sulphuric acid (2 × 5 ml) followed by 10% sodium carbonate solution (1 × 5 ml) and finally with water (5 ml). It was dried over sodium sulphate, solvents evaporated and residue distilled at 95-105°/5 min to yield (**8**) + (**9**), yield 10 g (67%); IR: 3500 (OH), 1725 (>C=O); PMR (CCl_4): δ 0.9 [d, 6H, J = 6.5 Hz, $-CH(CH_3)_2$], 1.1 (t, 3H, $-CH_2-CH_3$), 4.05 (q, 2H, $-O-CH_2$), 5.1-5.7 (2H, olefinic protons of **8** and **9**), 3.15 (1H, −OH, D_2O exchangeable).

2-(4-*Isobutylphenyl*)*ethyl propionate* (**10**)

Compounds (**8**) and (**9**) (2.54 g, 0.01 mole) were dissolved in dry toluene (100 ml) to which *p*-toluenesulphonic acid (2 g) was added and the mixture refluxed for 6 hr. The organic layer was washed with water, dried, solvents removed under reduced pressure and the residue was distilled at 105-110°/1 mm[6] to give **10**; yield 1.34 g (57%); IR: 1740 (>C=O); PMR(CCl_4): δ 0.9 [d, 6H, J = 6 Hz, $-CH-(CH_3)_2$], 1-1.5 (m, 6H, $-O-CH_2-CH_3$ and CH_3 CH−COOEt), 2.35 [d, 2H, $-CH_2-CH(CH_3)_2$], 1.85 [m, 1H, $-CH(CH_3)_2$], 3.6 (q, 1H, −CH−COOEt), 7.0 (aromatic protons), 4.0 (q, 2H, $-O-CH_2CH_3$); Mass spectrum: M^+ 234.

2-(4-*Isobutylphenyl*)*propionic acid* (*Ibuprofen*) (**11**)

Compound (**10**) (0.936 g, 0.004 mole) was dissolved in methanol (20 ml) to which was added 30% sodium hydroxide solution (4 ml). The mixture was refluxed for 4 hr, solvent removed under reduced pressure and the residue acidified with 3*N* hydrochloric acid. The solid separated was filtered and crystallised from benzene to yield **11**, 0.744 g (90%); IR: 1680 (C=O), 3260 (−OH); PMR ($CDCl_3$): δ 0.9 [d, 6H, J = 6 Hz, $-CH(CH_3)_2$], 1.4 [d, 3H, $CH_3-CH-COOH$)], 2.4 [d, 2H, $-CH_2-CH-(CH_3)_2$], 1.85 (m, 1H, $-CH(CH_3)_2$), 3.65 (q, 1H, $CH_3-CH-COOH$), 7.0 (aromatic protons). Mass spectrum: M^+ 206.

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4-Phenoxylongibornane/8-phenoxylongibornane from longifolene†

U R Nayak*, V S Dalavoy & V B Deodhar

National Chemical Laboratory, Pune 411 008

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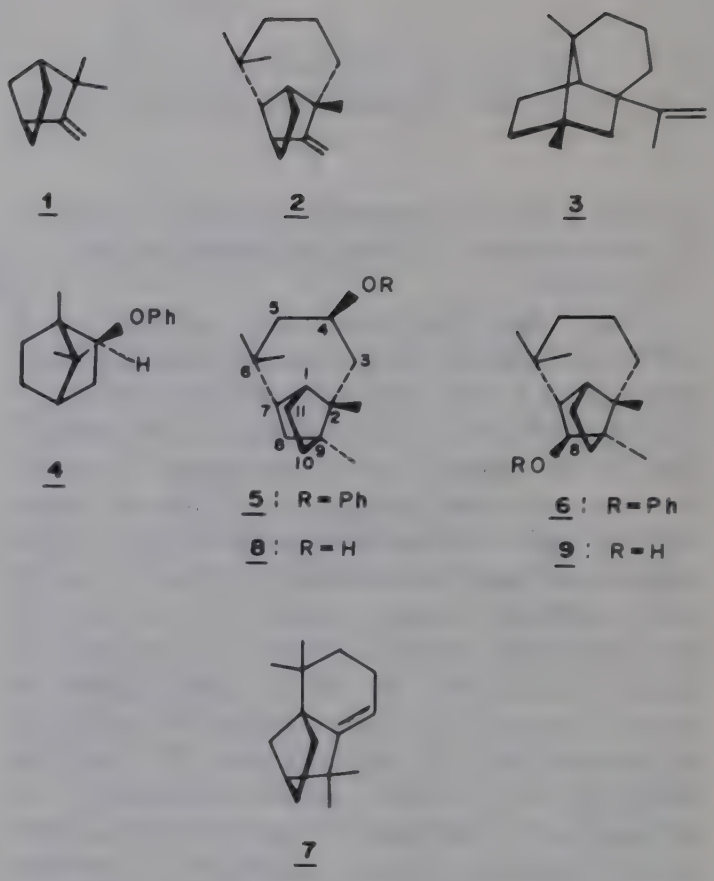
Boron trifluoride etherate-catalyzed condensation of phenol with camphene (**1**), longifolene (**2**) and alloisolongifolene (**3**) has been studied under comparable conditions: no reaction takes palce in the case of **3** while **1** and **2** give the phenoxy derivatives **4** and **5-6** in yields of 91% and 21% respectively. 4-Phenoxylongibornane (**5**)/8-phenoxylongibornane (**6**) have been separated and characterized.

Boron trifluoride etherate-catalyzed condensation of phenol with the vinylidene moieties in camphene[1] (**1**) and longifolene[2] (**2**) have been studied earlier. While investigating the chemistry of alloisolongifolene[3] (**3**), it appeared desirable to make a comparative study of the olefinphenol condensation on **3** along with **1** and **2**. The failure of **3** to give any phenoxy derivative notwithstanding, this note describes the separation and characterization of 4-phenoxylongibornane (**5**) and 8-phenoxylongibornane (**6**) for the first time in the longifolene-phenol condensation at 10°.

The condensation reaction when carried out at 10° (see Experimental) led, in the case of **1**, to the formation of isobornylphenyl ether (**4**) was to the extent of 91%. Longifolene (**2**) gave only 21% of the condensation product (*vide infra*) and the fore-run hydrocarbon was identified as isolongifolene (**7**), unavoidably formed from **2** because of exposure[4] to the Lewis acid. In the case of **3** there was practically no high-boiling condensation product and the entire distillate was found to be unchanged **3**.

By carrying out the longifolene-phenol (**2**) condensation at 0°, the earlier workers obtained[2] a mixture (yield 7%) of the phenoxy derivatives **5/6**, which were not separated but their structures only inferred after cleavage of the ethers mixture to the corresponding carbinols **8/9** with lithium in liquid ammonia. In the present case, however, by repeated chromatography of the reaction mixture over silica gel, it was possible to separate two pure compounds and characterize them on the basis of their PMR-multiplicity patterns (vide Experimental) of the α-proton on the carbon bearing the phenoxy group: the slightly faster-moving compound, 8-phenoxylongibornane (**6**) (involving a 1,2-shift) and the slower-moving major compound, 4-phenoxylongibornane (**5**) (involving a 1,2-shift followed by a 1,5-hydride transfer).



Experimental

Light petroleum refers to fraction, b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. IR spectra (ν_{max} in cm^{-1}) were recorded as smears on a Pye-Unicam SP-3 spectrophotometer; PMR spectra on a Varian T-60 spectrometer; mass spectra on a CEC spectrometer model 21-110B using an ionizing voltage 70 eV and a direct inlet system.

Condensation of longifolene (**2**) with phenol: 4-Phenoxylongibornane (**5**)/8-phenoxylongibornane (**6**)

A mixture of **2** (102 g, 0.5 mole) and phenol (47 g, 0.5 mole) was stirred vigorously in an ice-water bath (10°); $BF_3.OEt_2$ (1 ml) was added dropwise during 30 min and further stirred for 3 hr. The mixture was diluted with ether (200 ml), washed successively

†NCL Communication No. 4665

with 10% KOH (5 × 100 ml), water, brine, dried, solvent removed and the residue fractionally distilled: Fr I, isolongifolene[5], b.p. 100-105°/5 mm (75 g). Fr II, phenoxylongibornanes mixture **5-6**, b.p. 160°/1 mm (30.5 g, 21%).

Fr II (10 g) was chromatographed on silica gel /IIa (300 g; 95 cm × 3.5 cm) with TLC monitoring: Fr I, light petroleum, 3 × 100 ml, isolongifolene (**7**) (0.7 g); Fr 2, light petroleum, 5 × 100 ml, 8-phenoxylongibornane (**6**) (slightly impure; 2 g). Fr 3, light petroleum-benzene (1:1), 6 × 100 ml; 4-phenoxylongibornane **5** (pure).

Fr 2 (2 g) was rechromatographed on silica gel/IIa (100g,74cm × 1.8cm): Fr a, light petroleum, 6 × 100 ml, mixture. Fr b, light petroleum, 7 × 10 ml (pure).

4-Phenoxylongibornane (**5**): Colourless liquid b.p. 160°/1 mm (4.1 g). IR: 1595, 1580, 1240, 1000, 750, 690. PMR (CCl_4): δ 0.83, 0.93 × 2, 1.00 (four tertiary methyl singlets); 4.37 to 4.87 (essentially a septet, 1H, $-CH_2-CHOPh-CH_2-$); 6.67 to 7.33 (m, 5H, Ar − H). MS: m/z 298 (M^+). (Found: C, 85.0; H, 10.0. $C_{21}H_{30}O$ requires: , 84.5; H, 10.1%).

8-Phenoxylongibornane (**6**): Colourless liquid, b.p. 190° (bath)/0.5 mm (0.8 g). IR: 1595, 1580, 1240, 1040, 1110, 750, 690. PMR (CCl_4): δ 0.87, 0.97 (6H each, four tertiary methyl singlets); 4.55 (dd, 1H, $-CHOPh$); 6.77 to 7.40 (m, 5H, Ar − H). MS: m/z 298 (M^+) (Found: C, 85.1; H, 10.1. $C_{21}H_{30}O$ requires C, 84.5; H, 10.1%).

Condensation of camphene **1** with phenol: Isobornylphenyl ether (**4**)

Under the reaction conditions as described above, **1** (68 g, 0.5 mole) and phenol (47 g, 0.5 mole) gave **4** as a colourless liquid, b.p. 115°/1 mm (105 g, 91%) identified by IR/PMR.

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Two jasmonate-type cyclopentanone-based dimethyl esters from 10-undecenoic acid†‡

U R Nayak*, V B Deodhar & V S Dalavoy
National Chemical Laboratory, Pune 411 008

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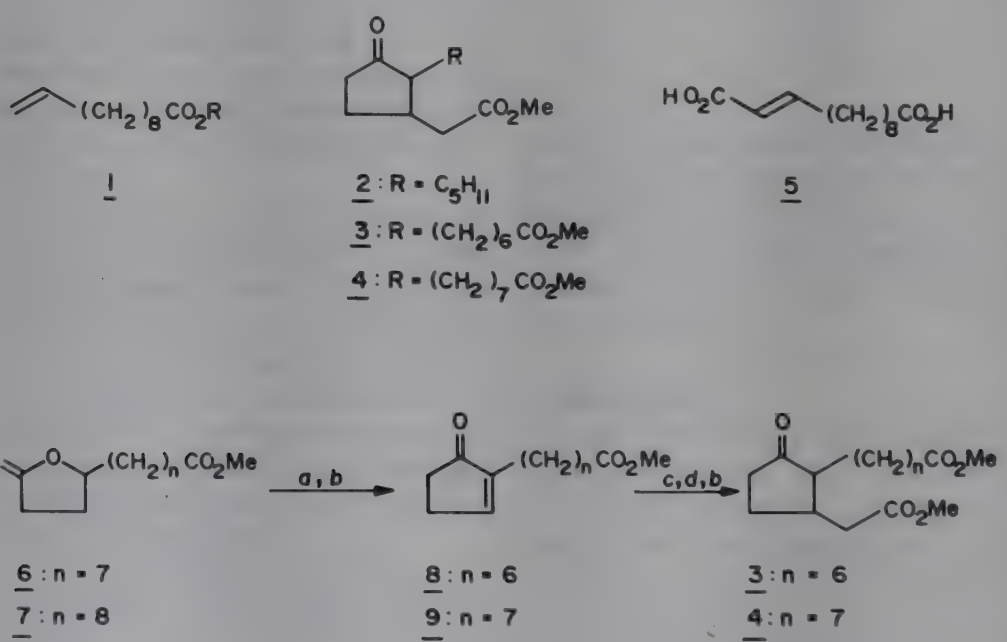
Reaction of methyl 10-undecenoate (**1**, R = Me) with manganic acetate gives homotraumatic lactone-ester (**7**) which on exposure to polyphosphoric acid generates the 2-substituted cyclopentenone (**9**). Michael reaction of **8**/**9** with diethyl malonate followed by saponification/decarboxylation/esterification affords the jasmonate-type cyclopentanone-based esters **3**/**4**.

Several compounds having some structural similarity with methyl dihydrojasmonate (**2**), an important commercial perfumery chemical, have been synthesized earlier[1]. Our own interest in the broader area of jasmonoids[2] now prompts us to describe the synthesis of two jasmonate-type cyclopentanone-based dimethyl esters **3**/**4** from 10-undecenoic acid[3] (**1**, R = H)—a pyrolysis product of castor oil; an abundant indigenous agricultural oil of commerce.

The general strategy employed, namely, lactone → cyclopentenone → cyclopentanone ester, is depicted in Scheme 1. Convenient methods for the preparation of traumatic acid[4] (**5**) traumatic lactone-ester[5] (**6**) from **1** (R = H) have been reported by us earlier. The conversion of an olefin to a γ-lactone with manganic acetate[6] when applied to methyl 10-undecenoate (**1**, R = Me) generated homotraumatic lactone-ester (**7**) in 31% yield. The lactone **6** has been earlier transformed[7] into the 2-substituted cyclopentenone **8**. On exposure of **7** to polyphosphoric acid (PPA) at 120°/1 hr, 3-oxo-cyclopenten-2-octanoic acid methyl ester (**9**) was formed in a low yield (20%). Michael addition of diethyl malonate[8] to **8**/**9** gave the corresponding adducts which were converted into the desired **3**/**4** via sa-



SCHEME 1

†NCL Communication No. 4670.
‡Jasmonoids: Part 2. For part 1 see ref. 2.

ponification-decarboxylation[9] followed by esterification.

Experimental

Light petroleum refers to fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. IR spectra (ν_{max} in cm^{-1}) were recorded as smears on a Pye-Unicam SP-3 spectrophotometer, PMR spectra on a Varian T-60 spectrometer and mass spectra on a CEC spectrometer model 21-110B using an ionizing voltage 70 eV and a direct inlet system.

Action of $Mn(OAc)_3$ on methyl 10-undecenoate (**1**, R = Me): Homotraumatic lactone-ester (**7**)

To a stirred mixture of $Mn(OAc)_2$ (49 g, 0.2 mole) in AcOH (260 ml) heated to 90°, was added $KMnO_4$ (6.4 g, 0.04 mole) in small portions. When the exothermic reaction subsided, Ac_2O (90 ml) was added followed by KOAc (100 g); methyl 10-undecenoate (**1**, R = Me; 20 g) was then added in one lot and the mixture refluxed with stirring under N_2 blanket until the dark brown colour of manganic acetate disappeared (2 hr). The mixture was diluted with water, extracted with light petroleum, washed successively with 5% aq. $NaHCO_3$, brine, dried, solvent removed and the residue chromatographed over silica gel/IIa (420 g; 60 cm × 5 cm) with TLC monitoring: Fr 1, benzene, 3 × 300 ml, recovered **1** (R = Me; 3.7 g, 19%); Fr 2, 10% EtOAc in benzene, 3 × 300 ml, mixture (0.98 g); and Fr 3, 10% EtOAc in benzene, 6 × 300 ml, pure.

Fr 3 was distilled to furnish **7** as a colourless liquid, b.p. 160°/1 mm (7.9 g, 31%); IR: 1770, 1730, 1180; PMR (CCl_4): δ 4.37 (broad ill-resolved t, 1H, $H_2C-CH-O-$), 3.63 (s, 3H, $COOCH_3$), 1.93 to 2.40 (4H, m, $2\times H_2C-CH_2-C=O$) (Found: C, 65.2; H, 9.5. $C_{14}H_{24}O_4$ required C, 65.6; H, 9.4%).

Action of PPA on **7**: Cyclopentenone **9**

P_2O_5 (98 g) was dissolved in H_3PO_4 (49 ml) and the resulting PPA was treated with **7** (7.8 g) and heated in an oil-bath at 120° with stirring for 1 hr. The dark brown mixture was poured onto crushed ice, extracted with EtOAc, washed with brine, dried, solvent removed and the residue esterified with 3% methanolic[10] HCl (50 ml) at room temperature (18 hr). The distilled product (b.p. 140°/1 mm, 2.4 g) was further purified by chromatography over silica gel/IIa (70 g, 60 cm × 2 cm): Fr 1, benzene, 5 × 75 ml, mixture (0.29 g); Fr 2, 10% EtOAc in benzene, 8 × 75 ml, pure; and Fr 3, 25% EtOAc in benzene, 6 × 75 ml, mixture (0.4 g).

Fr 2 was distilled to furnish **9** as a colourless liquid, b.p. 170° (bath)/1 mm (1.4 g, 20%); IR: 1730, 1695, 1670, 1640, 1200, 1170; PMR (CCl_4): δ 7.20 (bs, 1H, olefinic H), 3.67 (s, 3H, $COOCH_3$), 2.10 to 2.47 (m, 6H, $2\times H_2C-C=O$ and $H_2C-C=C$) (Found: C, 70.1; H, 9.6. $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.3%).

Michael addition of diethyl malonate to **9**: Cyclopentanone dimethyl ester (**4**)

A stirred solution of NaOEt[9] (from 0.22 g of Na in 20 ml of dry EtOH) was treated with diethyl malonate (8 g) and **9** (1.4 g). After stirring for 72 hr at room temperature the mixture was quenched in aq. AcOH, extracted with ether, washed with brine and dried. After removal of solvent and excess of diethyl malonate the residue was fractionally distilled: Fr 1, b.p. 170° (bath)/1 mm, recovered **9** (0.83 g, 59%); and Fr 2, free flame/1 mm, Michael adduct (0.54 g, 22%). A mixture of Fr 2 (0.48 g), conc. HCl (6.5 ml) and gl. AcOH (3.7 ml) was refluxed[9] for 16 hr (N_2 atoms).The mixture was diluted with water, extracted with EtOAc, washed with brine, dried, solvent removed and the residue esterified with 6% methanolic HCl (30 ml) at room temperature (18 hr) and the product distilled (free flame/0.5 mm) to yield **4** (0.32 g, 89%) as a pale yellow liquid; IR: 1730, 1170; PMR (CCl_4): δ 3.63 (s, 6H, $2\times COOCH_3$), 2.10 to 2.33 (m, 6H, $3\times H_2C-CH_2C=O$); MS: m/z 312 (M^+) (Found: C, 65.3; H, 9.1. $C_{17}H_{28}O_5$ requires C, 65.4; H, 9.0%).

Michael addition of diethyl malonate to the cyclopentenone **8**: Cyclopentanone ester (**3**)

A stirred solution of NaOEt (from 0.48 g of Na in 36 ml of dry EtOH) was treated with diethyl malonate (18 g) and the cyclopentenone **8** (3.5 g). After stirring for 96 hr at room temperature the mixture was acidified with dil. AcOH, extracted with ether, washed with brine and dried. After removal of solvent and excess of diethyl malonate the residue was fractionated: Fr 1, b.p. 180° (bath)/1 mm, recovered **8** (2.26 g, 63%); and Fr 2, free flame/1 mm, Michael adduct (2 g, 31%). A mixture of the adduct (2 g), conc. HCl (25 ml) and AcOH (15 ml) was refluxed for 14 hr under N_2. The mixture was worked up as before and the residue esterified with 6% methanolic HCl (50 ml) at room temperature overnight and the product distilled to furnish **3** as a pale yellow liquid, b.p. 210° (bath)/0.5 mm (1.2 g, 80%); IR: 1730, 1170; PMR (CCl_4): δ 2.13 to 2.40 (m, $3\times -CH_2CH_2-C=O$); 3.60 (s, 3H, $2\times COOCH_3$). MS: m/z 298 (M^+) (Found: C, 65.2; H, 9.2. $C_{16}H_{26}O_5$ requires C, 64.4; H, 8.8%).

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A facile synthesis of N-aryl-*N*-hydroxyformamides from N-arylhydroxylamines†

N R Ayyangar*, K C Brahme, M S Shingare & K V Srinivasan
National Chemical Laboratory, Pune 411 008

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Several N-arylhydroxylamines (2) have been formylated for the first time with acetic formic anhydride to yield N-hydroxyformanilides (3) in better yields than hitherto reported.

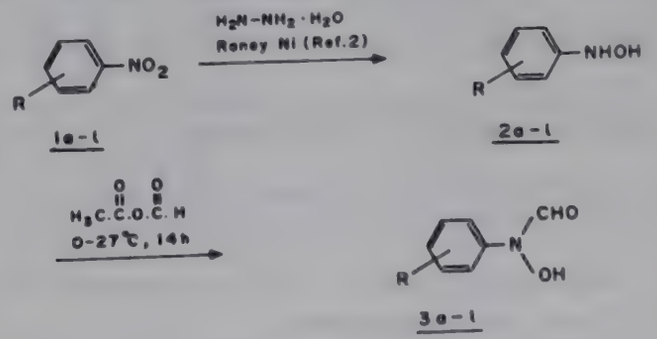
A selective transfer-reduction of nitroarenes to N-arylhydroxylamines has been recently reported by us[1]. We have also described the facile synthesis of *o*-chloroarylamines from nitroarenes by a novel *ortho*-halogenation reaction on N-substituted benzo- and aceto-hydroxamic acids[2-4]. The innovative application of the above methodologies for the synthesis of clonidine, an anti-hypertensive drug, has been described by us in a recent communication[5]. This synthesis of clonidine involved N-(2-chlorophenyl)-N-hydroxyformamide as a key intermediate which was required in good yields to improve the overall process economics. Moreover, N-aryl-N-hydroxyformamides as a class have shown promising biological activities[6-11], and have been widely used as analytical precipitants for extraction and estimation of several metals[12]. In view of this we attempted to evolve an efficient formylation method for their synthesis. This note describes the formylation of N-arylhydroxylamines for the first time with acetic formic anhyride to yield N-aryl-N-hydroxyformamides in better yields than hitherto reported.

N-Hydroxy-N-phenylformamide was first prepared in about 13% yield by the reaction of formic acid with N-phenylhydroxylamine[13]. Later on N-arylhydroxylamines were treated with formic acid and dicyclohexylcarbodiimide to get N-aryl-N-hydroxyformamides in 30-50% yield[14-18]. Substituted aromatic nitroso compounds have been shown to react rapidly with glyoxylic acid in aq. methanolic solutions to form N-aryl-N-hydroxyformamides in yields ranging from 47-81%. However, it was further shown that N-arylhydroxylamines which are precursors of the nitroso compounds did not yield any hydroxamic acid with glyoxylic acid, formaldehyde, formic or oxalic acid[18].

We were looking for an easy-to-prepare and highly efficient formylating agent for use at laboratory temperature conditions. Formyl chloride, because of its lowest ability under these conditions (stable for 1 hr at −60°), was discarded. We chose acetic formic anhydride as the formylating agent due to its high reactivity and easy preparation. Although this reagent has been widely used for formylating a variety of organic compounds[19-22], much to our surprise, extensive literature survey on the synthetic methods for N-aryl-N-hydroxyformamides did not reveal the use of this formylating agent.

Acetic formic anhydride was prepared according to the method described in experimental section and was used as soon as it was prepared. The required substituted N-arylhydroxylamines (2a-1) were prepared from the corresponding nitroarenes (1a-1) by transfer reduction, and formylated to the desired N-hydroxyformanilides (3a-1) with the above reagent (Scheme 1).

In initial attempts, the reagent was prepared using commercially available 85% formic acid. Although this reagent works well for the formylation of substituted aromatic amines to give the corresponding formanilides in excellent yields (85-100%)[23], it was not found suitable for the formylation of N-arylhydroxylamines. In our reactions, we obtained a poor yield of the N-hydroxyformanilides with simultaneous formation of substantial amounts of tarry material. This may be due to the instability of the N-arylhydroxylamines which may undergo Bamberger and related rearrangements in the presence of large excess of acetic acid. The generation of excess of acetic acid is



Scheme 1

†NCL Communication No. 4376

caused by the presence of water in 85% aq. formic acid. Hence, in our subsequent attempts, acetic formic anhydride was prepared from 100% formic acid.

In preliminary experiments, the N-arylhydroxylamine was added slowly during 0.5 hr to the acetic formic anhydride so as to maintain the temperature at 40°. These experiments also resulted in very poor yields of the formylated products; in some cases there was no formylation at all. This may be attributed to: (a) the instability of the hydroxylamine at 40°, and (b) presence of two alternative sites of formylation giving rise to N-formylated and N,O-diformylated products in the presence of excess formylating agent at 40°.

Formylation of N,O-dibenzoyl derivatives during benzoylation of N-arylhydroxylamines either in the presence of excess benzoyl chloride or when equimolar amount of benzoyl chloride was used at temperatures above 10°, has been observed by us[1].

Therefore, in the final refinement of the method, acetic formic anhydride was added dropwise to a solution of 2 in solvent ether at 0°. the reaction was then carried out for 14 hr at 27°. The N-hydroxyformanilides were isolated by a series

Table 1—Characterization data of N-hydroxyformanilides (3)

Compd	Ar	Yield[a] (%)	m.p.[b] °C	Mol. formula[c]	MS (m/z)	PMR
3a	C_6H_5	75	70 (70)[18]	—	—	—
3b	2-ClC_6H_4	60	80	$C_7H_6ClNO_2$	173(27%), 171(83), 155(30), 143(100), 128(67), 127(78), 99(59), 90(47), 75(21).	7.2-7.5(m,4H,Ar-H), 8.6(s,1H,CHO), 10.4 (s,1H, exchangeable with D_2O, OH)
3c	3-ClC_6H_4	50	129 (129)[18]	—	—	—
3d	4-ClC_6H_4	70	123 (123)[18]	—	—	—
3e	4-BrC_6H_4	75	126 (122-22.5)[18]	—	—	—
3f	2-H_3C-C_6H_4	50	72 (72-73)[18]	—	—	—
3g	3-H_3C-C_6H_4	60	85	$C_8H_9NO_2$	151(38%), 135(35), 107(32), 106(100), 105(53), 104(48), 92(18), 91(32), 79(20).	2.3(s,3H,CH_3), 6.9-7.3 (m,4H,Ar-H), 8.3(s, 1H,CHO).
3h	4-H_3C-C_6H_4	61	105 (105.5-6.5)[18]	—	—	—
3i	2-CH_3O-C_6H_4	45	105	$C_8H_9NO_3$	167(28%), 151(13), 139(100), 135(5), 122(57), 120(94), 108(30), 106(33).	3.8(s,3H,OCH_3),6.9-7.5 (m,4H,Ar-H),8.3(s, 1H,CHO), 9.2 (s, 1H, exchangeable with D_2O, OH).
3j	4-CH_3O-C_6H_4	52	77 (75-77)[18]	—	—	—
3k	3-O_2N-C_6H_4	50	142	$C_7H_6N_2O_4$	182(12%), 166(3) 154(14), 137(18) 136(30), 108(17), 98(100).	7.4-7.9 (m,3H,Ar-H), 8.3 (s,1H,Ar-H),8.6 (s,1H,CHO), 10.8 (s, 1H, exchangeable with D_2O, OH).
3l	1-$C_{10}H_7$	75	160	$C_{11}H_9NO_2$	187(99%), 169(10), 143(23), 142(44), 141(44), 140(44), 128(25), 115(100).	7.3-7.5 (m,4H,Ar-H), 7.7-7.9 (m,3H,Ar-H), 8.3 (s,1H,CHO), 10.4 (s,1H, exchangeable with D_2O, OH).

[a]Isolated yield.

[b]Lit. m.ps are given in parentheses.

[c]Satisfactory microanalyses were obtained: C ± 0.22, H ± 0.15 and N ± 0.32%.

of extraction procedures described in the experimental section. The crude products were purified by crystallization from benzene- pet. ether (40°-60°). All the N-hydroxyformanilides (**3a-l**) gave a characteristic violet colour with alcoholic ferric chloride. All the compounds were characterised by their spectral data and elemental analyses (Table 1).

Features of the present method are: (i) First systematic study of the formylation of N-arylhydroxylamines using acetic formic anhydride, (ii) better yields of N-hydroxyformanilides than hitherto reported for the formylation of N-arylhydroxylamines and (iii) use of 100% formic acid for preparing the formylating reagent and the mode of addition playing a key role in reducing the Bamberger and related rearrangements thereby improving the selectivity of the process.

Experimental

Melting points are uncorrected. IR spectra were recorded in nujol on a Pye-Unicam SP3-100 infrared spectrophotometer, PMR spectra in $CDCl_3$ on a Varian 80A FT-NMR spectrometer using TMS as internal sandard (chemical shifts in δ, ppm), and mass spectra on a Finnigan MAT-1020 automated GC/MS instrument.

Preparation of acetic formic anhydride

To the cooled (at 0°) and well stirred acetic anhydride (10.2 g, 0.1 mole) was added formic acid (100%) (4.6 g, 0.1 mole) dropwise during 10 min, and the mixture slowly heated to 50°, stirred at 50° for 2 hr and cooled. The reagent was used immediately for formylation reaction.

Reduction of nitroarenes (**1**) to N-arylhydroxylamines (**2**)

It was carried out by the method already reported by us[1].

Formylation of N-arylhydroxylamines (**2**) to N-aryl-N-hydroxyformamides (**3**): General procedure.

N-Arylhydroxylamine (0.1 mole) was dissolved in sodium-dried ether (100 ml) and cooled to 0°. Acetic formic anhydride (0.2 mole)[prepared from acetic anhydrides (20.4 g, 0.2 mole) and formic acid (9.2 g, 0.2 mole)] was added to it dropwise with vigorous stirring during 0.5 hr, and the stirring continued without external cooling for 14 hr. The reaction mixture was then neutralised with sodium carbonate (10% w/v) (350 ml), and the ether layer separated. The aq. layer was saturated with common salt and extracted thrice with 100 ml portions of ether. The combined ether extract was shaken with sodium hydroxide solution (10% w/v) (50 ml). The alkaline layer was separated and the ether layer washed with water. The alkaline layer and the water washings were combined and acidified with HCl (10% w/v) (50 ml). The acidic solution was saturated with common salt, and the separated N-hyroxyformanilide (**3**) filtered. The filtrate was extracted thoroughly with ether. The ether layer was separated, dried over sodium sulphate, and the solvent removed by distillation to yield more of **3**. The crude product (**3**) was crystallized from benzene-pet. ether (1:1). The characterization data of **3** are recorded in Table 1.

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One-step synthesis of thiazolo[4,5-*d*]pyrimidines

V K Ahluwalia*, Shashibala, Rachna Aggarwal & R Chandra†
Department of Chemistry, University of Delhi, Delhi 110 007

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One-step synthesis of thiazolo[4,5-*d*]pyrimidines involves reaction of different thiobarbituric acids with N-bromosuccinimide and thiourea in the presence of benzoyl peroxide. Thiazoles and pyrimidines are associated with multifarious activities. Thiazolo[4,5-*d*]pyrimidines are very good antifungal and antibacterial compounds. They are found to have good inhibitory activity in nucleotides.

Thiazoles[1-3] and pyrimidines[4-6] individually or in combination (such as thiazolopyrimidines[7,8]) constitute a group of compounds of biological interest. A multistep synthetic strategy for thiazolopyrimidines is reported in literature[8]. Herein we report a one-step synthesis of thiazolo[4,5-*d*]pyrimidines in good yield (75-80%). This reaction involves *in situ* formation of bromopyrimidines by the reaction of N-bromosuccinimide (NBS) on thiobarbituric acids followed by condensation with thiourea to give the corresponding thiazolopyrimidines.

Thus, 2-thiobarbituric acid (**1**) on reaction with NBS, benzoyl peroxide and thiourea at reflux temperature in benzene gave 5-amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-*d*]pyrimidine (**2**). Similar condensation of 1,3-diarylthiobarbituric acids (**3-7**) afforded 1,3-diaryl-5-amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-*d*]-pyrimidines (**8-12**). Structure of all these compounds have been confirmed on the basis of ^1H NMR spectral data and elemental analyses. The presence of $-NH_2$ group was confirmed by synthesising benzoyl (**13, 14**) and acetyl derivatives (**15-18**).

The characterization data of compounds synthesised are listed in Table 1.

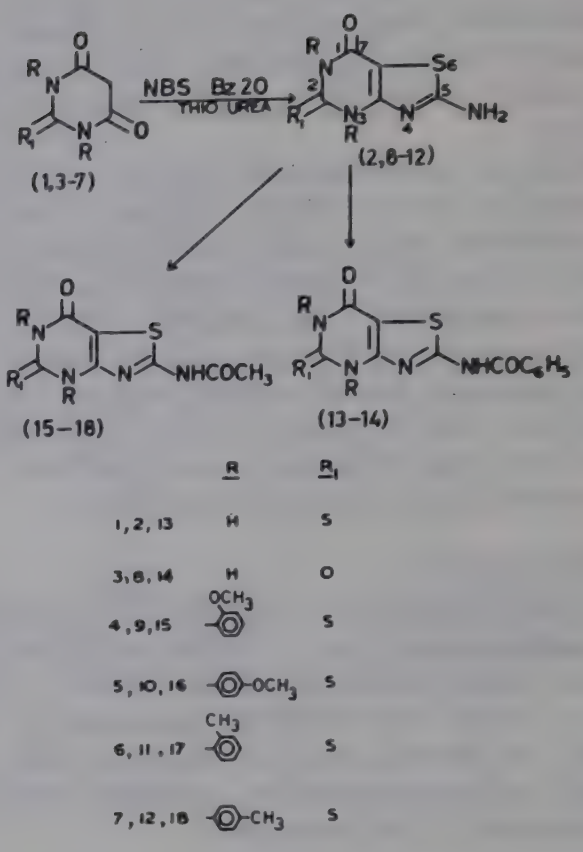

Table 1—Spectral data of compounds **8-18**

Compd[a]	Yield (%)	m.p. (°C)	Mol. formula (M^+)
8	78	260-61	$C_5H_4N_4O_2S$
9	75	205-6	$C_{19}H_{16}N_4O_3S_2$
10	78	200-201	$C_{19}H_{16}N_4O_3S_2$
11	80	196-97	$C_{19}H_{16}N_4OS_2$
12	82	255-56	$C_{19}H_{16}N_4OS_2$
13	80	280-90	$C_{12}H_8N_4O_2S_2$
14	70	280-81	$C_{12}H_8N_4O_3S$
15	68	300	$C_{21}H_{18}N_4O_4S_2$
16	72	300	$C_{21}H_{18}N_4O_4S_2$
17	71	300	$C_{21}H_{18}N_4O_2S_2$
18	80	210-11	$C_{21}H_{18}N_4O_4S_2$

[a]Satisfactory microanalyses were obtained for all the compounds.

Experimental

5-Amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-*d*]-pyrimidine (**2**)

A mixture of **1** (1 g) and NBS (1.2 g) was refluxed with thiourea (0.054 g) and benzoyl peroxide (0.05 g) in benzene (40-50 ml) at reflux temperature for 4-5 hr. The solvent was distilled off under reduced pressure and the residue treated with crushed ice. Hydrobromide thus obtained was treated with potassium carbonate solution (5%) to liberate the free amino compound (**2**) as yellow solid, which was crystallized from benzene-pet. ether as yellow nee-

†UGC Research Scientist

dles (0.8 g), yield 80%; m.p. 195-96°; $C_5H_4N_4OS_2$; ^1H NMR ($CDCl_3$): 7.90 (bs, 2H, D_2O exchangeable $-NH_2$).

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Synthesis of spiro-pyrazolines: Reaction of 1,3-diphenylnitrilimine with 5-oxazolones

R Raghunathan* & P V Rajagopal Naidu
Department of Chemistry, Govt. College Nandanam, Madras 600 035

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A one-step synthesis of a new series of spiro-pyrazolines (**4-6**) has been accomplished by 1,3-dipolar cycloaddition of 1,3-diphenylnitrilimine to 4-arylidene-5-oxazolones (**1-3**).

The concept of 1,3-dipolar cycloaddition has been well utilised in the synthesis of heterocyclic compounds by a one-step process[1,2]. Diphenylnitrilimine, a classic example of reactive 1,3-dipole[2-5] and 5-oxazolones have been used in the synthesis of novel heterocyclic systems[6]. In view of the synthetic and mechanistic importance of the cycloaddition of 1,3-dipoles, we have investigated the reaction of 4-arylidene-2-phenyl-5-oxazolones with 1,3-diphenylnitrilimine.

Diphenylnitrilimine, generated in benzene solution at room temperature by the addition of triethylamine on benz-N-phenylhydrazidoyl chloride, underwent a clean reaction with 5-oxazolones (**1-3**) to give exclusively novel spiro compounds (**4-6**), the 1:1 adducts as shown by TLC and M^+ peak in the mass spectra (Scheme 1). The reaction period varied depending on the nature of arylidene group in 5-oxazolones.

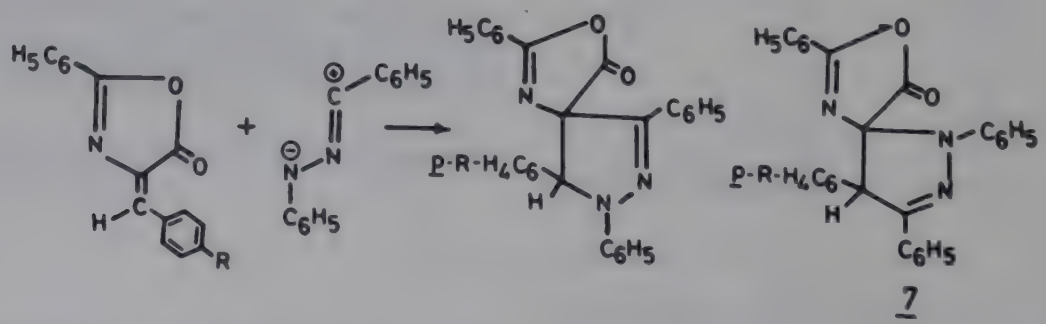
Thus, 4-benzylidene-2-phenyl-5-oxazolone (**1**) reacted at room temperature with diphenylnitrilimine for 28 hr to give **4** which showed an absorption band at 360 nm in UV spectrum characteristic of pyrazoline structure. Its IR spectrum exhibited peaks at 1785 and 1805 of unequal intensity attributed to the lactone carbonyl and at 1640 cm^{-1} due to C=N function indicating that the addition of the dipole had taken place across the exocyclic double bond of the oxazolone. The addition may be expected to result in the formation of either the regioisomer **4** or **7**. However, based on the chemical shift of the methine proton of pyrazoline moiety, the product was assigned the structure **4**.

The PMR spectrum of **4** exhibited a multiplet at δ 7-7.7 (20H) due to aromatic protons and a singlet at 5.3 (1H) due to benzylic methine proton. Had the addition of dipole taken place in the opposite direction to give the isomer **7** the benzylic proton would have appeared as a singlet at δ 3.2[7,8]. The structure was also supported by its mass spectral data.

Experimental

Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 580 spectrophotometer, PMR spectra in $CDCl_3$ on a Bruker 90 MHz instrument using TMS as internal standard, UV spectra in methanol on a Varian Cary 170 spectrophotometer, and mass spectrum on an F Mat 8230 spectrometer at 70 eV.

Benz-N-phenylhydrazidoyl chloride was prepared by literature procedure[2] and oxazolones were obtained following the procedure as described in reference 9.



1 R = H
2 R = Cl
3 R = CH_3

4 R = H
5 R = Cl
6 R = CH_3

7

Scheme 1

Reaction of 5-*oxazolones* (**1-3**) *with* 1,3-*diphenylnitrilimine: General procedure*

To a solution of an appropriate oxazolone (1 mmole) and N-phenylbenzhydrazidoyl chloride (1 mmole) in dry benzene was added triethylamine and the reaction mixture stirred well until the starting material had disappeared (28, 22, and 36 hr for **1, 2**and **3** respectively as revealed by TLC). After the reaction was over the solution was filtered to remove triethylamine hydrochloride. The filtrate on evaporation *in vacuo* yielded a crude solid which on crystallisation from methanol gave the pure product. All the compounds, thus prepared, gave satisfactory elemental analysis. Other characterization data are given below:

4: m.p. 130-32°, yield 63%; UV: 370, 360, 290 nm, MS: m/z 443 (M^+) 415 ($M^+ - CO$) 399 ($M^+ - CO_2$), 340 ($M^+ - C_6H_5C\equiv N$), 296 ($399 - C_6H_5CN$), 194 ($296 - C_6H_5 - C\equiv CH$)$^+$ 119 ($C_6H_5-\overset{O}{\underset{\diagdown\diagup}{C}}=N)^{+\cdot}$, 103 ($C_6H_5C\equiv N)^{+\cdot}$, 91 ($194 - C_6H_5C\equiv N)^{+\cdot}$ and 77 $(C_6H_5)^+$.

5: m.p. 164-66°, yield 70%; IR: 1805, 1785 (C=O), 1625 (C=N), 1590 cm^{-1} (C=N); UV: 370, 355, 280 nm; PMR: δ 7.0-8.1 (m, 19H, Ar−H), 5.3 (s, 1H, benzylic C−H); MS: m/z 477 (M^+), 449, 433, 374, 330, 194, 103, 91 and 77.

6: m.p. 143-44°, yield 60%; IR: 1805, 1780 (C=O), 1610 (C=N), 1575 cm^{-1} (C=N); UV: 375, 350, 285 nm, PMR: δ 6.6-8.0 (m, 19H, Ar−H), 5.3 (s, 1H benzylic C−H), 1.1 (s, 3H, CH_3); MS: 457 (M^+), 429, 413, 354, 310, 194, 103, 91 and 77.

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Synthesis of 4-methylpyrano[2,3-*a*] xanthone

R S Konde Deshmukh & M V Paradkar*
Department of Chemistry, Post-Graduate and Research Centre, Abasaheb Garware College, Karve Road, Pune 411 004

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4-Methylpyrano[2,3-*a*]xanthone (**1**) has been synthesised by reaction of 1-hydroxy-2-acetylxanthone (**3**) with the Wittig reagent, $Ph_3P=CHCOOEt$.

In connection with our work on oxygen heterocycles, we required the title compound for its further transformation into a linear tetracyclic system. Condensation of 4-methyl-7-hydroxycoumarin with ethyl salicylate in diphenyl ether[1] was earlier reported to give **1** (m.p. 280°). However its structure remained unsupported because of lack of spectral data. We could not repeat their experiment and in our hands only the starting materials were recovered. It was thus thought appropriate to synthesise **1** starting with a preformed xanthone nucleus through the Wittig reaction[2,3].

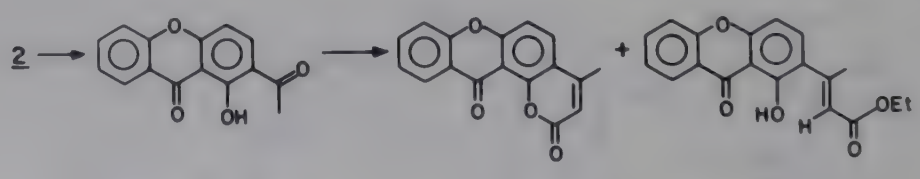
The starting 1-hydroxy-2-acetylxanthone (**3**) was obtained in better yield by reacting 1-hydroxyxanthone (**2**)[4] with acetic anhydride instead of acetyl chloride as reported[5]. Compound **3** reacted with carbethoxymethylene triphenylphosphorane by heating at 150-60° for 24 hr to yield a phenolic product (10%) and a neutral product (52%). The neutral product was identified as **1** and the phenolic product as **4** from their spectral and analytical data. Incidentally the remote possibility of formation of **5** involving participation of xanthone carbonyl in the Wittig reaction was also ruled out as follows; **2** on reaction with $Ph_3P=CHCOOEt$ under similar conditions remained intact. Thus this indicates that the product obtained (m.p. 259°) is the required **1** and the reported m.p. 280° for **1** appears in error.

Experimental

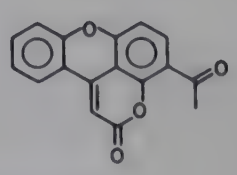
All the m.ps are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 337 IR spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a 90 MHz Perkin-Elmer R-32 instrument using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm) and mass on Finnigan MAT1020, automated GC/MS instrument at 70 ev.

4-Methylpyrano[2,3-a]xanthone (**1**)

A mixture of **3** (1.0 g, 0.004 mole) and Wittig reagent (1.4 g, 0.004 mole) was heated at 150-60° for 24 hr. The reaction mixture was cooled and triturated with methanol (5 ml). The solid thus separated was filtered and chromatographed on a silica gel column. Elution with benzene afforded unreacted **3** (0.05 g, 5%). Further elution with benzene/ethyl acetate (1:1) afforded a solid which crystallised from chloroform to yield **1** (0.460 g, 52%), m.p. 259° (Found: C, 73.2; H, 3.8. $C_{17}H_{10}O_4$ requires C, 73.4; H, 3.6%); IR: 1740, 1680, 1600 cm^{-1}; PMR ($CDCl_3$): δ 2.48 (3H,d,CH_3), 6.33(1H,q,H-3′), 7.37-7.8 (3H,m,Ar-H-5, H-6,H-7), 7.42(1H,d,J = 8Hz, H-4), 7.91(1H, d,J = 8Hz,H-3), 8.37(1H,dd,J = 8Hz,2Hz,H-8); MS: m/z 278 (M^+, 80%), 250(100%). The methyl alcohol filtrate was concentrated and the residue



and not **5**



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purified by chromatography using benzene as solvent. First fraction gave **4** (0.100 g, 10%), m.p. 142°; IR: 1715, 1640, 1620-10; PMR: δ 1.33(3H, t,J = 7Hz, -$COOCH_2CH_3$), 2.57(3H,s, olefinic CH_3), 4.22(2H,q,J = 7Hz, -$COOCH_2CH_3$), 6.17(1H,s,olefinic H), 6.97(1H,d,J = 8Hz,H_4), 7.25-8.4(5H,m,Ar-H), 13.48(1H,s,D_2O exchangeable, -OH); MS; m/z 324 (M^+, 14%), 279(8%), 251(100%). The second fraction furnished additional quantity of **3** (0.150 g, 15%).

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Cyclodehydrogenation of 2′-hydroxychalcones and dehydrogenation of flavanones using nickel peroxide

Uttam K Mallik, Murari M Saha & Asok K Mallik*
Department of Chemistry, Jadavpur University, Calcutta 700 032

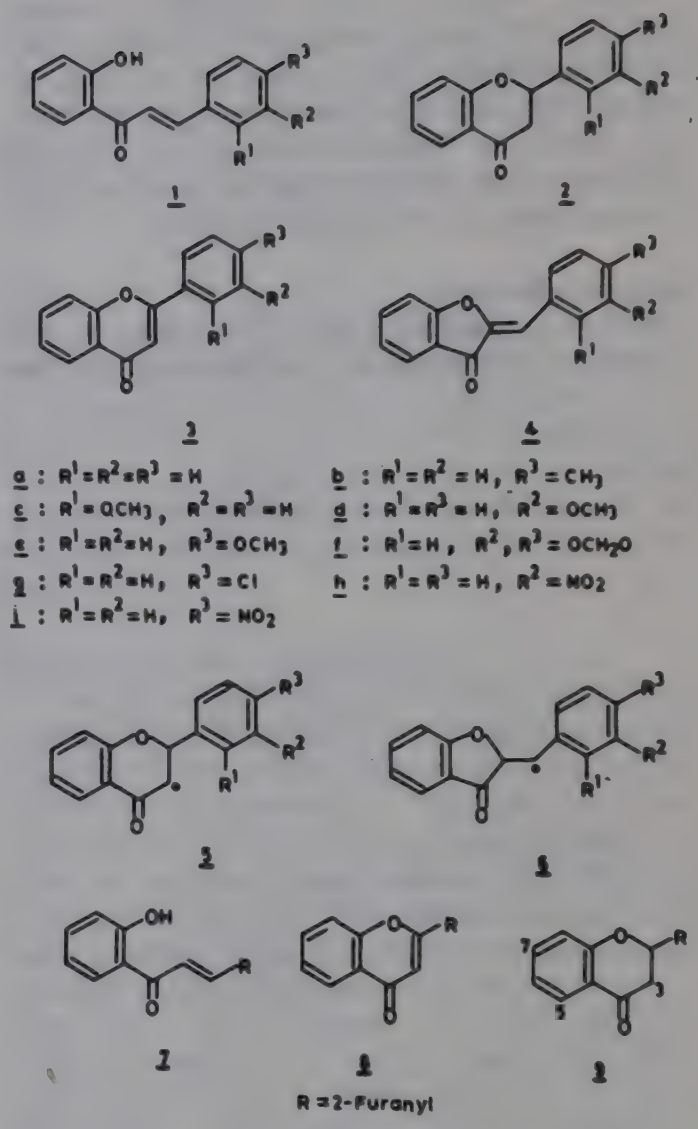
Received 13 October 1988; accepted 15 March 1989

Nickel peroxide oxidation of 2′-hydroxychalcones (**1**) gives flavones (**3**) in moderate yields, aurones (**4**) are also formed in cases where the 2/4 position of the starting **1** bears either a strong π-donor or a π-acceptor substituent. Flavanones (**2**) are dehydrogenated with this reagent to the corresponding flavones (**3**) in very good yields.

Different reagents have been used for the cyclodehydrogenation of 2′-hydroxychalcones (**1**)[1-12] and depending upon the reagent used flavones, aurones and isoflavones are formed either singly or as a mixture. Dehydrogenation of flavanones (**2**) to flavones (**3**) has also been accomplished by several reagents[1,13-15]. The applicability of nickel peroxide for cyclodehydrogenation of 2′-hydroxychalcones (**1**) and dehydrogenation of flavanones (**2**) has been presently investigated as this reagent possesses usefulness in some other cyclodehydrogenation and dehydrogenation reactions[16].

The reaction of **1** with nickel peroxide either in boiling benzene or in dioxane at 100° afforded flavones (**3**) in all cases and aurones (**4**) in some cases. Flavanones (**2**) were also obtained from most of the 2′-hydroxychalcones (**1**) (Table 1). Nickel peroxide caused dehydrogenation of flavanones (**2**) in refluxing benzene giving flavones (**3**) in very good yields (Table 2). Attempted reactions of **1** and **2** with nickel peroxide at room temperature however did not meet with success.

The results in Table 1 show that aurone formation takes place only when **1** contains either a strong π-donor or a π-acceptor substituent at the 2/4 position. These results may be rationalised in the following way by considering the involvement of OH radical[16,17]. The OH radical induced cyclisation of **1** may take place in two ways leading to the radicals **5** and **6**, which in turn lead to **3** (from **5**) and **4** (from **6**). Although **5** appears to be sterically more favoured than **6**, the relative stabilities of these two radicals would be dependent on the substituents[18]. Thus, **5** is stabilised to the same extent in all the cases by conjugation with >C=O but **6** is stabilised significantly only when it is generated from **1** bearing either a strong π-donor or a π-acceptor substituent at 2/4 position. Hence aurones are formed in these cases only. Facile reaction in dioxane compared to that in benzene may be due to the higher reaction temperature and/or easy formation of **5** and **6** owing to the possibility of intermolecular H-bonding of **1** with dioxane.



Treatment of **7**, a heterocyclic analogue of **1**, with nickel peroxide (dioxane, 100°, 18 hr) yielded two products which have been characterised as 2-(2-furanyl)chromone (**8**) (12%) and 2-(2-furanyl) chromanone (**9**) (6%).

Experimental

Melting points reported are uncorrected. All crystallisations were from chloroform-pet ether (60-80°). The IR spectra were recorded in nujol on a Perkin-Elmer 297 spectrophotometer, the PMR spectra in $CDCl_3$ on a JEOL FX 100 spectrometer with TMS as an internal standard, Nickel peroxide was prepared from nickel sulphate and alkaline

Table 1—Products of nickel peroxide oxidation of 2′-hydroxychalcones(**1**)[a,b]

Substrate	Solvent[c]	Yields (%)[d] of products		
		3	**4**	**2**
1a	B	18	—	2
	D	42	—	5
1b	B	13	—	4
	D	38	—	6
1c	B	5	3	—
	D	13	6	—
1d	B	11	—	Trace
	D	46	—	—
1e	B	12	5	5
	D	48	12	4
1f	B	9	2	Trace
	D	32	10	10
1g	B	20	—	Trace
	D	43	—	6
1h	B	16	—	Trace
	D	54	—	—
1i	B	11	4	—
	D	40	10	—

[a] Reaction time was 18 hr except in the case of **1d** and **1h** in dioxane when the reaction was completed in 12 hr.

[b] In cases of reactions in benzene 20-27% of **1** remained unchanged.

[c] B = Benzene, D = Dioxane.

[d] Based on the amount of starting 2′-hydroxychalcone (**1**).

Table 2—Nickel peroxide induced dehydrogenation of flavanones (**2**) in benzene under reflux[a]

Flavanone	Reaction time (hr)	Yield (%) of **3**
2a	10	83
2b	6	71
2c	8	72
2d	8	76
2e	8	79
2f	10	71
2g	6	81
2h	6	84
2i	6	86

[a] Trace amount of isomeric 2′-hydroxychalcone also resulted in cases of **2e** and **2f**.

sodium hypochlorite[19] and the available oxygen content of its different samples was in the range 2.5-3.0 mg atom/g.

2′-Hydroxychalcones (**1a-i**) were prepared by condensing *o*-hydroxyacetophenone with appropriate benzaldehyde in aqueous ethanolic alkali as reported in the literature[20-22]; m.ps (°C): **1a** 88-89 (lit.[12] 88-90): **1b** 119-20 (lit.[23] 119); **1c** 113-14 (lit.[12] 112-14); **1d** 94-95 (lit.[12] 94); **1e** 93-94 (lit.[12] 92-94); **1f** 136-38 (lit.[3] 137-38); **1g** 150-51 (lit.[12] 148-51); **1h** 163-65 (lit.[21] 164-65); **1i** 208 (lit.[21] 209).

Compound **7**, m.p. 100-102° (lit.[24] 99°), was also prepared[22] similarly.

Flavanones (**2a-i**) were obtained by acid-catalysed cyclisation of 2′-hydroxychalcones (**1**) as described in the literature[21,25]; m.ps (°C); **2a** 76-77 (lit.[12] 74-75); **2b** 68-70 (lit.[25] 69-71); **2c** oil[12]; **2d** 78-79 (lit.[12] 78-79); **2e** 95-97 (lit.[12] 96-98); **2f** 125-26 (lit.[8] 127-28); **2g** 85-87 (lit.[12] 85-86); **2h** 141-42 (lit.[20,21] 142); **2i** 166-67 (lit.[21] 166-67).

General procedure for cyclodehydrogenation of 2′-hydroxychalcones (**1**)

To a solution of **1** (2 mmole), either in benzene or in dioxane, nickel peroxide containing 5 mg atom available oxygen was added, half at the beginning and the rest after 8 hr of reaction. The reaction mixture was heated in a boiling water-bath with stirring and filtered after the time mentioned in Table 1. The residue was washed with chloroform-methanol to obtain high polar product, if any. The filtrate and washings were combined. The crude product mixture obtained by removal of solvent was chromatographed over silica gel using petroleum ether-ethyl acetate of increasing polarity as eluants. The sequence in which different crystalline compounds were obtained was unreacted chalcone (**1**), flavanone (**2**), aurone (**4**), flavone (**3**) and these were followed by some amorphous materials; m.ps (°C); **3a** 98-99 (lit.[12] 96-98); **3b** 110-12 (lit.[11] 111-12); **3c** 100-102 (lit.[12] 101-3); **3d** 129-30 (lit.[12] 127-29); **3e** 156-57 (lit.[12] 156-58); **3f** 200 (lit.[8] 199-200); **3g** 188-90 (lit.[12] 188-89); **3h** 202 (lit.[20] 201-2); **3i** 243-44 (lit.[11] 241-43); **4c** 173-75 (lit.[12] 173-75); **4e** 137-38 (lit.[11] 137-38); **4f** 190-91 (lit.[3] 190); **4i** 207-8 (lit.[11] 206-8).

For **7** also the above procedure was followed. The products were **8**, m.p. 134-35° (lit.[26] 135°), and **9**, m.p. 77-78°; PMR: δ2.98 [1H, dd, J = 17 & 4 Hz, H-3 (eq)], 3.30 [1H, dd, J = 17 & 11 Hz, H-3 (ax)], 5.57 (1H, dd, J = 11 & 4 Hz, H-2), 6.36-6.56 (2H, m, H-3 & H-4 of furan), 6.96-7.16 (2H, m, H-6 & H-8), 7.42-7.62 (2H, m, H-5 of furan and H-7) and 7.94 (1H, dd, J = 8.2 & 2 Hz, H-5).

General procedure for dehydrogenation of flavanones (**2**)

To a solution of **2** (2 mmole) in benzene, nickel peroxide containing 5 mg atom available oxygen was added and the mixture was heated in a boiling water-bath with stirring for 6-10 hr. Work-up of the reaction mixture as in the case of **1** afforded flavones (**3**).

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Reaction of steroidal epoxides with BF_3-etherate

Shafiullah* & Malik Jamaluddin

Steroid Research Laboratory, Department of Chemistry, Aligarh Muslim University, Aligarh 202 002

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3β-Chloro-5,6α-epoxy-5α-stigmastane (**1**) and its 3β-hydroxyderivative (**2**) on treatment with BF_3-etherate afford the ketones (**3** and **4**), the backbone rearranged products (**5** and **6**), Westphalen rearranged products (**7** and **8**) and flourohydrins (**9** and **10**). The structures of these products have been established on the basis of their analytical and spectral data.

A number of papers dealing with the BF_3-etherate catalysed rearrangements of steroidal epoxides have been reported in the literature[1-4]. Simplicity in carrying out the reaction at ambient temperature and formation of noble backbone and Westphalen rearranged products prompted us to study the reaction of steroidal epoxides (**1**) and (**2**) in stigmastane series with BF_3-etherate. Earlier we have studied different reactions[5-8] on compounds in the cholestane series.

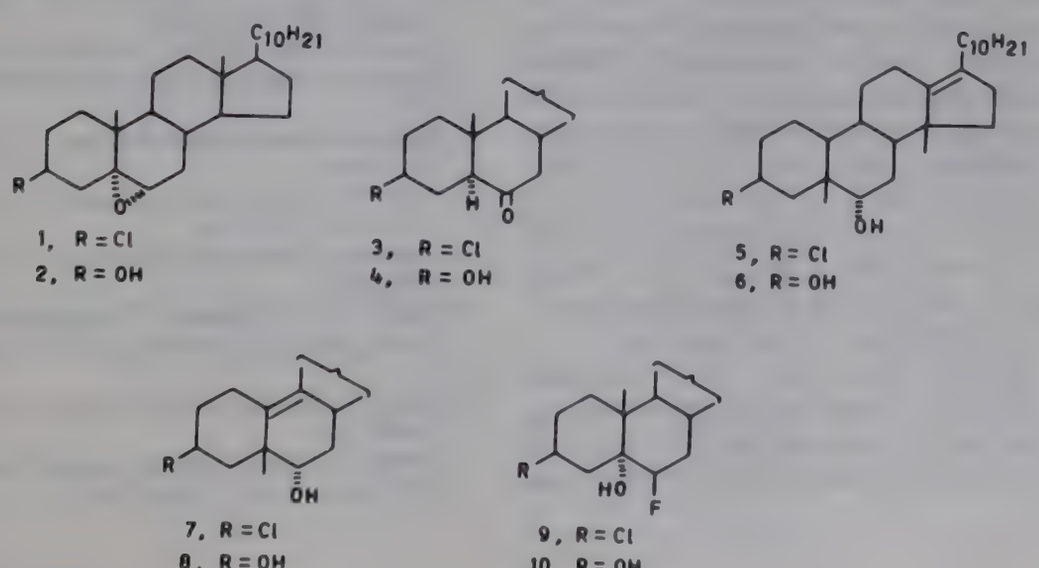
The reaction of BF_3-etherate with 3β-chloro-5,6α-epoxy-5α-stigmastane (**1**) afforded 3β-chloro-5α-stigmastan-6-one (**3**), 3β-chloro-5β,14β-dimethyl-18,19-bisnor-10α-stigmast-13(17)-en-6α-ol (**5**), 3β-chloro-5β-methyl-19-nor-stigmast-9(10)-en-6α-ol (**7**) and 3β-chloro-6β-fluoro-5α-stigmast-5α-ol (**9**). Under similar reaction conditions 3β-hydroxy-5,6α-epoxy-5α-stigmastane (**2**) gave 3β-hydroxy-5α-stigmastan-6-one (**4**), 3β-hydroxy-5β-14β-dimethyl-18,19-bisnor-10α-stigmast-13(17)-en-6α-ol (**6**), 3β-hydroxy-5β-methyl-19-nor-stigmast-9(10)-en-6α-ol (**8**) and 3β-hydroxy-6β-fluoro-5α-stigmast-5α-ol (**10**). Structures of these products were supported by their elemental analysis and spectral data. The mechanism of their formation has already been reported in the literature[1-4].

Experimental

Reaction of epoxide (1) *with* BF_3*-etherate*

3β-Chloro-5,6α-epoxy-5α-stigmastane (**1**) (4 g, 8.9 m mol) in benzene (280 ml) was treated with BF_3-etherate (4 ml, .032 mol) and kept at 20° for 7 min. The solution was poured into 5% $NaHCO_3$ solution, the mixture diluted with ether and washed with water. The ethereal solution was dried over Na_2SO_4. Evaporation of the solvent left an oil that was chromatographed on a silica gel column (80 g). The column was successively eluted with 40:1, 20:1, 15:1 and 5:1, mixtures of light petroleum and ether to give fractions I-IV, respectively.

Fraction I provided 3β-chloro-5α-stigmastan-6-one (**3**) as an oil which was crystallized from methanol, yield 0.975 g (2.17 m mol; 24.4%), m.p. 78° (Found: C, 77.5; H, 10.9. $C_{29}H_{49}ClO$ requires C, 77.5; H, 11.0%); gave positive Beilstein test; IR(nujol): 1710 (>C=O), 760 cm^{-1} (C−Cl); PMR($CDCl_3$): δ 3.85 (1H, brm, $W_{\frac{1}{2}}=17$ Hz, $C_3\alpha-H$) (axial, A/B ring junction *trans*), 0.93,



1, R = Cl
2, R = OH

3, R = Cl
4, R = OH

5, R = Cl
6, R = OH

7, R = Cl
8, R = OH

9, R = Cl
10, R = OH

0.83, 0.73, 0.63 (each s, angular and side chain methyl protons).

Fraction II afforded 3β-chloro-5β,14β-dimethyl-18,19-bisnor-10α-stigmast-13(17)-en-6α-ol (**5**) as a non crystallizable oil, yield 0.725 g (1.61 m mol; 18.1%) (Found: C, 77.6; H, 11.0. $C_{29}H_{49}ClO$ requires C, 77.5; H, 11.0%); gave positive Beilstein test; IR(nujol): 3420 (−OH), 760 cm^{-1} (C−Cl); PMR ($CDCl_3$): δ 3.88 (1H, brm, $W_{\frac{1}{2}}$ = 8 Hz, $C_3\alpha-H$), 4.37 (1H, m, $W_{\frac{1}{2}}$ = 7 Hz, $C_6\beta-H$), 2.65 (1H, s, OH, exchangeable with deuterium), 2.45 (1H, m, C_{20}-allylic-H)[10], 1.12 (3H, s, $C_5\beta-CH_3$)[10], 0.93 (3H, s, $C_{14}\beta-CH_3$), 0.86, 0.82 (each s, other methyl protons).

Fraction III furnished 3β-chloro-5β-methyl-19-nor-stigmast-9(10)-en-6α-ol (**7**) as a colourless solid which was recrystallized from acetone, yield 0.765 g (1.70 m mol, 19.2%), m.p. 142° (Found: C, 77.5; H, 11.0. $C_{29}H_{49}ClO$ requires C, 77.5; H, 11.0%); gave positive Beilstein test; IR(nujol): 3410 (−OH), 760 cm^{-1} (C−Cl); PMR ($CDCl_3$): δ 3.78 (1H, brm, $W_{\frac{1}{2}}$ = 8 Hz, $C_3\alpha-H$)[11], 4.42 (1H, m, $W_{\frac{1}{2}}$ = 7 Hz, $C_6\beta-H$), 2.62 (1H, s, OH, exchangeable with deuterium), 1.28 (3H, s, $C_5\beta-CH_3$)[11], 0.78 (3H, s, $C_{13}\beta-CH_3$)[11], 0.92, 0.86 and 0.82 (each, s, other methyl protons).

Fraction IV gave 3β-chloro-6β-fluoro-5α-stigmast-5-ol (**9**) as a noncrystallizable oil, yield 0.835 g (1.85mmol,20%)(Found:C,75.0;H,10.8.$C_{29}H_{50}ClFO$ requires C, 74.2; H, 10.8%); gave positive Beilstein test; IR (nujol): 3420 (−OH), 760 (C−Cl), 745 cm^{-1} (C−F); PMR ($CDCl_3$): δ 3.82 (1H, brm, $W_{\frac{1}{2}}$ = 17 Hz, $C_3\alpha-H$)[9], 4.26 (1H, m, $W_{\frac{1}{2}}$ = 4 Hz, $C_6\alpha-H$), 2.58 (1H, s, OH, exchangeable with deuterium), 0.93, 0.83, 0.73, 0.63 (each s, other angular and side chain methyl protons).

Reaction of epoxide (**2**) *with* BF_3*-etherate*

3β-Hydroxy-5,6α-epoxy-5α-stigmastane (**2**) (4 g, 9.2 m mol) under similar reaction conditions as mentioned above and column chromatography afforded 3β-hydroxy-5α-stigmastan-6-one (**4**) on elution with pet. ether-ether (20:1) as a solid which was recrystallized from methanol, yield 0.925 g (2.91 m mol, 23.12%), m.p. 132° (Found: C, 80.8; H, 11.8. $C_{29}H_{50}O_2$ requires C, 80.9; H, 11.7%); IR (nujol): 3420 (−OH), 1705 cm^{-1} (>C=O); PMR ($CDCl_3$): δ 5.01 (1H, m, $W_{\frac{1}{2}}$ = 17 Hz, $C_3\alpha-H$), (axial, A/B ring junction *trans*)[9], 0.93, 0.83, 0.73, 0.63 (each s, methyl protons).

Elution with pet. ether-ether (10:1) furnished 3β-hydroxy-5β,14β-dimethyl-18,19-bisnor-10α-stigmast-13(17)-en-6α-ol (**6**) as an oil, yield 0.735 g (1.70 m mol, 18.37%)(Found: C, 81.0; H, 11.8. $C_{29}H_{50}O_2$ requires C, 80.9; H, 11.7%); IR(nujol): 3410 cm^{-1} (−OH); PMR ($CDCl_3$): δ 5.02 (1H, m, $W_{\frac{1}{2}}$ = 8 Hz, $C_3\alpha-H$)[10], 4.52 (1H, m, $W_{\frac{1}{2}}$ = 7 Hz, $C_6\beta-H$), 2.65 (1H, s, OH, exchangeable with deuterium), 2.43 (1H, m, C_{20}-allylic proton)[10], 1.12 (3H, s, $C_5\beta-CH_3$)[10], 0.93 (3H, s, $C_{14}\beta-CH_3$), 0.88, 0.86, 0.82 (each s, other methyl protons).

Elution with pet. ether-ether (5:1) provided 3β-hydroxy-5β-methyl-19-nor-stigmast-9(10)-en-6α-ol (**8**) as an oil, yield 0.775 g (1.77 m mol, 19.37%) (Found: C, 80.9; H, 11.8. $C_{29}H_{50}O_2$ requires C, 80.9; H, 11.7%); IR(nujol): 3415 (−OH); PMR($CDCl_3$): δ 5.01 (1H, m, $W_{\frac{1}{2}}$ = 8 Hz, $C_3\alpha-H$), 4.53 (1H, m, $W_{\frac{1}{2}}$ = 7 Hz, $C_6\beta-H$), 2.45 (1H, s, OH, exchangeable with deuterium), 1.32 (3H, s, $C_5\beta-CH_3$)[4], 0.78 (3H, s, $C_{13}\beta-CH_3$)[4], 0.92, 0.86, 0.82 (each, s, other methyl protons).

Further elution with pet. ether-ether (1:1) gave 3β-hydroxy-6β-fluoro-5α-stigmast-5α-ol (**10**) as an oil, yield 0.815 g (1.89 m mol, 19.37%) (Found; C, 77.3; H, 11.5. $C_{29}H_{51}FO_2$ requires C, 77.3; H, 11.4%); IR (nujol): 3420 (−OH), 740 cm^{-1} (C−F); PMR ($CDCl_3$): δ 5.05 (1H, m, $W_{\frac{1}{2}}$ = 16 Hz; $C_3\alpha-H$)[9], 4.16 (1H, m, $W_{\frac{1}{2}}$ = 4 Hz, $C_6\beta-H$), 2.42 (1H, s, OH, exchangeable with deuterium), 0.93 (3H, s, $C_{10}-CH_3$), 0.63 (3H, s, $C_{13}-CH_3$), 0.83, 0.73 (each, s, other methyl protons).

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Acetoxylation of friedelin by lead (IV) acetate and anti-octant behaviour of 2-acetoxyketones

G Dutta & S N Bose*
Department of Chemistry, North Bengal University, Darjeeling 734 430

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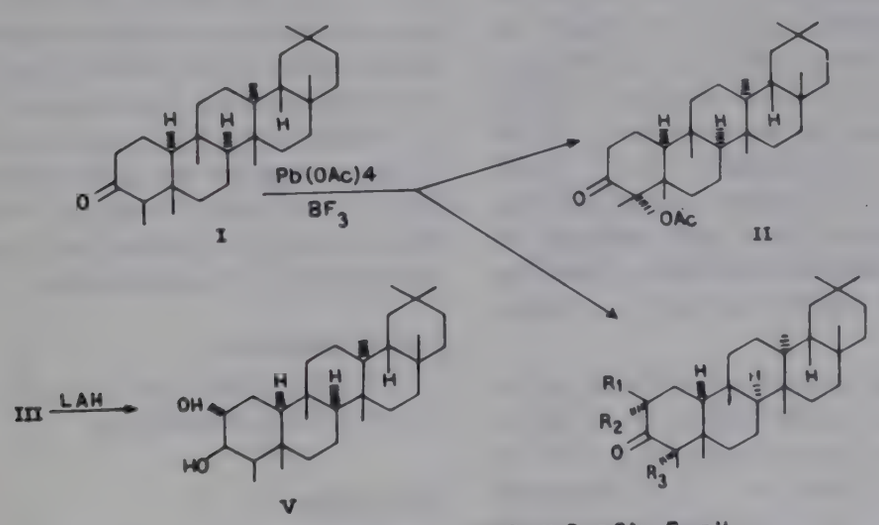
Four products have been isolated by boron trifluoride-catalysed lead (IV) acetate acetoxylation of friedelin. Three of them have been characterised as 2α-acetoxyfriedelin, 4α-acetoxyfriedelin and 2β, 4α-diacetoxyfriedelin. The former has been efficiently converted into pachysandiol-A. Chiroptical measurements (CD) of these 2-acetoxyketones show considerable anti-octant behaviour.

Acetoxylation of carbonyl compounds by lead (IV) acetate is a well-documented process having a great synthetic potential[1]. It has been extensively studied in steroidal 3-ketones and tetracyclic and pentacyclic triterpenoids bearing a 4,4-dimethyl-3-ketone moiety. The reaction is believed to proceed through the enol form and markedly catalyzed by boron trifluoride[2]. The pentacyclic triterpene ketone, friedelin (I) would serve as an interesting candidate for this acetoxylation reaction because the ketone group is flanked by α-methylene on one side and α′-methine on the other giving rise to two different enols. Recently, in connection with the structure elucidation of 2α-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid Kumar and coworkers[3] reported briefly the lead tetraacetate reaction of 3-oxocanophylate, a friedelin derivative, and isolated two products 2α-acetoxy and 4α-acetoxy compounds from this reaction. Herein, we wish to report the isolation of four products from the lead (IV) acetate reaction of friedelin, and use of one of them for a short convenient synthesis of pachysandiol-A. We also report the CD measurements of these 2-acetoxyketones, which showed considerable anti-octant behaviour.

Friedelin (I), obtained from petroleum extract of cork waste, was treated with Pb(IV) acetate in acetic acid solution in the presence of boron trifluoride etherate at room temperature for 3 hr. The crude product was subjected to chromatography on silica gel. The least polar product (24%) eluted in petroleum-benzene (5:1) was crystallised from chloroform-methanol to furnish II as needles, m.p. 290°, $[\alpha]_D$ −45.0° (*c* 1, chloroform), $C_{32}H_{52}O_3$ (M^+ 484). Its IR spectrum (nujal) showed bands at 1740 and 1260 ($OCOCH_3$) and 1725 cm^{-1} (CO). PMR spectrum (100 MHz, $CDCl_3$, TMS) exhibited signals at δ 2.15 (3H, s, $OCOCH_3$), 2.35 (2H, m, $-CH_2CO-$), 1.6 (3H, s, 23-CH_3) and six saturated tertiary methyl groups between 1.25 and 0.82. The mass spectrum (70 eV, direct) showed a strong molecular ion peak at m/z 484 (M^+, 65%) and other prominent peaks at 442(92), 424 ($M^+ - ACOH$, 100), 398(10), 341(12), 205(65) and 176(14). The absence of acetate methine proton established the structure of this



product as 4-acetoxyfriedelin (II). Based on the known preference of attack of the acetate ion on the intermediate organolead salt from the less hindered α-face[4] of the molecule the stereochemistry of the acetate group was assigned α.

The second product (22%) eluted in petroleum-benzene (5:2) was crystallised from chloroform-methanol to afford fine needles, $C_{32}H_{52}O_3$ (M^+, 484), m.p. 256-8°, $[\alpha]_D$ −29°. The structure of this product was established as 2α-acetoxyfriedelin (III; cerin acetate) by direct comparison with acetylation product of cerin. The formation of this product is also consistent with the preferred attack of the acetate ion from the less hindered α-face[3].

The third product (28%) isolated from petroleum-benzene (1:1) eluate was crystallised from chloroform-methanol as needles m.p. 290°, $C_{34}H_{54}O_5$. Its IR spectrum showed bands at 1750, 1730, 1242 ($OCOCH_3$) and 1720 cm^{-1} (CO). The PMR spectrum gave signals for two acetoxy groups at δ 2.16 (3H, s, $OCOCH_3$) and 2.06 (3H, s, $OCOCH_3$). The protons of one methyl group appeared at δ 1.69 (3H, s, C-23 CH_3) and those of six saturated tertiary methyl groups between 1.25 and 0.88. The acetate methine proton appeared at δ 3.72 (1H, dd, −COCHOAc−). The considerable upfield shift of the acetate methine proton could be attributed to the shielding by the carbonyl group in the distorted 2,4-diacetoxy-3-keto ring-A of this product. An inspection of the molecular model supports this view. The mass spectrum registered the highest peak at m/z 482 (M^+ − AcOH, 26%). Assignment of the configuration of the acetoxy groups at C-2 and C-4 was based on chemical conversions. This diacetoxy compound could be prepared either from 2β-acetoxyfriedelin (IV) (epicerin acetate) or from 4-α-acetoxyfriedelin (II), but not from 2α-acetoxyfriedelin (III) (cerin acetate) under the same conditions of boron trifluoride-catalysed Pb(IV) acetate reaction. Thus, the stereostructure of this compound was established as 2β,4α-diacetoxyfriedelin (VII). Besides monoacetoxylation, α,α′-diacetoxylation where such positions are available is also reported to occur in many cases[1a]. α-Acetoxyketones may react to furnish α, α′-diacetoxy compounds[5].

The most polar material (4% yield) eluted in petroleum-benzene (1:4) was crystallised from chloroform-methanol as fine microcrystals, m.p. 250°. Its IR spectrum exhibited bands at 1750, 1250 (acetate) and 1700 cm^{-1} (CO). Studies are underway for the complete characterization of this minor product.

Partial synthesis of pachysandiol-A(V)

Pachysandiol-A(V) (friedelane-2α,3β-diol) was isolated from *Pachysandra terminalis*[6]. Later on it was partially synthesised[7] from friedelin (I) by a sequence of reactions involving LAH reduction, benzoylation, pyrolytic elimination, epoxidation. followed by acid-catalysed epoxide cleavage. We have now carried out a short and convenient synthesis of this compound. 2α-Acetoxyfriedelin (III), one of the major products of lead (IV) acetate acetoxylation of friedelin (I), on lithium aluminium hydride reduction furnished V in high yield (76%).

Chiroptical measurement

Circular dichroism (CD) measurement of friedelin (I) in dioxane showed a negative cotton effect (CE) at 290 nm ($\Delta\varepsilon = -2.68$) and cerin acetate, 2α-acetoxyfriedelin (III), in the same solvent also showed negative CE $\Delta\varepsilon = -1.47$ at 300 nm. An examinatiion of the octant diagram revealed that 2α-acetoxy substituent (axial) lies in the back lower-left octant and hence should make more negative contribution than that of the parent ketone (I), but actually it makes less negative contribution. This anti-octant behaviour of 2-acetoxyketones has been studied in steroids and other types of compounds[8,9]. In 2β-acetoxyfriedelin (epicerin acetate; IV), obtained by acid-catalysed epimerization of III, the substituent 2β-acetoxy group (equatorial) lies almost in the nodal plane and has practically little contribution. This has been reflected in its CD spectrum, $\Delta\varepsilon = -2.36$ at 298 nm (dioxane), almost the same as that of friedelin mentioned above. ORD spectra of III and IV were recorded by Kikuchi and Toyoda[6], but their anti-octant behaviour was not studied. The anti-octant behaviour was also observed in II which showed a negative CE [$\Delta\varepsilon = -3.17$ at 300 nm (dioxane)]. In II, 4β-methyl group lies in the nodal plane making no contribution but 4α-acetoxy group which lies in back lower-right octant should make positive contribution but actually it makes negative contribution thereby making CE more negative in comparison to the parent ketone (I). In short, 2-acetoxy-3-keto derivatives of friedelane show significant anti-octant behaviour as reflected in CD measurements.

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Oxidation of 10-methoxy-9-anthraldehyde with various oxidising agents in protic and aprotic media

P K Sen*, Sikha Lahiri, Gautam Chattopadhyay & Dipak K Mandal

Department of Chemistry, Presidency College, Calcutta 700 073

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Treatment of 10-methoxy-9-anthraldehyde (**5**) with various oxidising agents in protic and aprotic media fails to produce 10-methoxy-9-anthranoic acid (**4**), instead 9,10-anthraquinone is obtained in most cases. The effect of acid/alkali on **5** itself also gives rise to 9,10-anthraquinone and a trace of anthrone. Attempted decarbonylation of 9-methoxyanthracene-10-ketocarboxylic acid (**7**) fails to give the desired **4**.

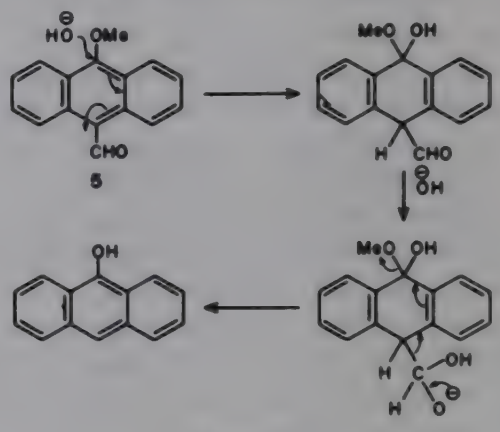
Aryl participation in the formation of spirodienones with the substrates **1b-d** have been developed earlier[1]. But Ar 1-3 participation with **1a** could not be accomplished as the diazoketone could not be prepared from the parent acid. To minimise the steric interference at the two *ortho* positions of the cyclising moiety and to increase the nucleophilicity at the cyclising centre for effective Ar 1-3 participation reaction we required the diazoketone (**2**) and hence needed 10-hydroxyanthracene-9-carboxylic acid (**3**) which might in turn be obtained from 10-methoxy-9-anthraldehyde (**5**) by oxidation followed by demethylation.

9-Methoxyanthracene (**6**) was prepared[2] from anthrone in an improved yield of 58% and converted into **5**[3] in 84% yield. Attempts were made to prepare 10-methoxy-9-anthranoic acid (**4**) from **5** using variety of oxidising agents in protic and aprotic media and by alkali fusion method[5]. Jones' reagent, $KBrO_3$ in acidic medium[6] and "non-aqueous" chromium (V) complex[7], $(Bipy)H_2CrOCl_5$, all afforded 9,10-anthraquinone. The same product was obtained by alkali fusion method[5]. **5**, however, resisted oxidation with alkaline silver oxide and also by pyridinium dichromate[8]. These results led us to study the effect of acid/alkali only on **5**. Treatment of **5** with alcoholic KOH and glacial acetic acid-HCl separately furnished 9,10-anthraquinone alongwith a trace of anthrone and unreacted aldehyde (*vide* Experimental).

1
a, x = 0
b, x = 1
c, x = 2
d, x = 3

2, R = H, R' = $COCHN_2$
3, R = H, R' = CO_2H
4, R = Me, R' = CO_2H
5, R = Me, R' = CHO
6, R = Me, R' = H
7, R = Me, R' = $COCO_2H$

As regards the oxidation of **5** to 9,10-anthraquinone our findings are in agreement with the mechanism proposed elsewhere[4]. However, the mechanism of transformation of **5** to 9,10-anthraquinone under the action of acid/base appears to be uncertain. The formation of 9,10-anthraquinone even under inert atmosphere ruled out aerial oxidation of intermediate anthrone, although it may be possible that anthrone might be formed under basic condition according to the pathway shown in Scheme 1.



SCHEME 1

In another approach, attempted decarboxylation of the keto acid (**7**) obtained by the reaction of **6** with oxalyl chloride gave back **6** instead of the desired acid (**4**). **7** also remained unchanged on treatment with alkaline hydrogen peroxide[9].

Experimental

Melting points are uncorrected. PMR spectra were recorded on a Varian EM-390 instrument; chemical shifts are expressed in δ (ppm) with TMS as an internal standard. IR and mass spectra were recorded on Pye-Unicam SP 3-300S spectrophotometer and 70 eV Hitachi RMU 6L instrument respectively. All analytical results are within experimental error. Petroleum ether refers to the fraction 60-80°.

9-Methoxyanthracene (**6**)

To a refluxing solution of anthrone (20 g, 0.103 mole) in absolute ethyl alcohol (140 ml) was added, in portions, aq. NaOH (12 g in 40 ml of water) and

methyl *p*-toluenesulphonate (36 g in 20 ml of ethyl alcohol) successively. The reaction mixture was refluxed for 1 hr, poured in cold water, the precipitate collected and chromatographed (alumina) to afford pure **6** (12.5 g, 58%), m.p. 96°.

10-*Methoxy*-9-*anthraldehyde* (**5**)

To a mixture of **6** (10 g, 0.048 mole) and dimethylformamide (11 ml) was added dropwise phosphorous oxychloride (10.5 ml) with stirring and, the mixture heated on a water-bath for 1 hr. It was poured into ice-cold water containing sodium acetate the precipitate obtained collected and crystallised from ethanol to yield **5** as yellow crystalline solid (9.5 g, 84%), m.p. 160°.

Oxidation of **5** with Jones' reagent

Jones' reagent (1 ml, prepared from 3.5 g of CrO_3 in 8 ml water, 3 ml conc. H_2SO_4 and diluted to 15 ml) was added dropwise to a solution of **5** (1 g, 0.004 mole) in acetone (55 ml) kept at about 5°. Stirring was continued for further 7 hr at room temperature, excess oxidising agent destroyed by dropwise addition of isopropyl alcohol and filtered. After usual work-up, the residue afforded 9,10-anthraquinone as pale yellow needles (toluene), m.p. 284°, identical (m.m.p., IR) with anthentic sample.

Oxidation of **5** with chromium (V) complex, $(Bipy)H_2CrOCl_5$

To the bipyridyl complex (0.77 g, 1.9 mmole) was added a solution of **5** (0.15 g, 0.635 mmole) in CH_2Cl_2 (8 ml) under N_2 atmosphere and the reaction mixture stirred for 12 hr at room temperature. it was then chromatographed (silica gel/pet ether) to afford a mixture (identified by co-TLC) containing unreacted **5** and 9,10-anthraquinone. The latter was obtained as pale yellow needles (benzene) and characterized as before.

Fusion of **5** with alkali mixture

A mixture of **5** (1 g, 0.004 mole) and fused slurry of alkali [97% NaOH (0.7 g, 0.017 mole) and 84% KOH (0.8 g, 0.012 mole)] was maintained at 200-20° (bath temp.) for 30 min with stirring. The mixture was extracted with water and filtered. The filtrate on acidification did not give any carboxylic acid. After chromatography (alumina) the residue afforded 9,10-anthraquinone.

Treatment of **5** with alcoholic KOH

5 (0.5 g, 0.002 mole) was refluxed with alc KOH (0.3 g, 50 ml ethanol) for 6 hr. The mixture was diluted with water, neutralized and extracted with ether. After usual work up, the residue was chromatographed (alumina). Elution with pet ether afforded a mixture of unreacted **5** and a trace of anthrone (cO-TLC). Further elution with pet ether-benzene (1:1) gave 9,10-anthraquinone which was characterized as before.

No significant change in product composition was observed when the reaction was performed under nitrogen atmosphere.

Treatment of **5** with acid (HOAc + HCl)

5 (0.5 g, 0.002 mole) was refluxed with gl acetic acid (10 ml) and conc. HCl (3 drops) for 12 hr. After work up as above, a similar product composition was found.

9-Methoxyanthracene-10-ketocarboxylic acid (**7**)

To a solution of **6** (5 g, 0.024 mole) in dry carbon disulphide (30 ml) cooled to 10-15° was added dropwise with stirring a solution of oxalyl chloride (3.5 g, 3 ml, 0.027 mole) in dry carbon disulphide (20 ml). The reaction mixture was refluxed for 1 hr, poured onto crushed ice, extracted with CCl_4, organic layer washed with water and finally extracted with aq. NaOH. The alkaline extract was acidified to afford **7** as a yellow solid (1.6 g, 23%), m.p. 146-48°. Purification by alkali-acid treatment raised the m.p. to 148-50°. IR(KBr): 1670 (C = O) and 1700 (CO_2H); PMR ($CDCl_3$): δ 8.2-8.5 (*m*, 2H), 7.8-8.1 (*m*, 2H); 7.2-7.7 (*m*, 4H); 4.,2 (*s*, 3H, OCH_3); 6.44 (*bs*, 1H, $COCO_2H$, D_2O exchangeable); Mass: 280/M^+, 252, 235, 208, 193.

7 (0.2 g) on heating at 150° for 30 min afforded **6**, m.p. 96°, identical (co-TLC, IR) with an authentic sample.

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Synthesis of (*Z*)-5-dodecenyl and (*Z*)-5-tetradecenyl acetates: Pheromone components of *Lepidoptera noctuidae* species†

S V Kelkar, G Bhaskar Reddy & G H Kulkarni*
National Chemical Laboratory, Pune 411 008
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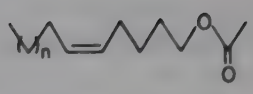
(*Z*)-5-Dodecenyl acetate (**1**) and (*Z*)-5-tetradecenyl acetate (**2**), the pheromone components of *Lepidoptera noctuidae* species have been synthesised by a new approach from the corresponding (*Z*)-4-undecenol (**3**) and (*Z*)-4-tridecenol (**4**), both of which have been obtained from a common intermediate, viz. the dianion of 4-pentyn-1-ol.

(*Z*)-5-Dodecenyl acetate (**1**) and (*Z*)-5-tetradecenyl acetate (**2**) have been identified as the main components of sex pheromone of *Lepidoptera noctuidae*[1,2]. The acetates (**1**) and (**2**) have also been isolated from the absolute oil of *Hibiscus abelmoschus* Linn[3]. A number of syntheses of **1** and **2** have been reported[4-6].

We now report an alternate synthetic approach for **1** and **2** via the known (*Z*)-4-alkenols (**3**) and (**4**) which in turn were prepared from the dianion of 4-pentyn-1-ol as per the reported procedure[7].

(*Z*)-4-Undecen-1-ol (**3**) was converted into the bromide (**7**) via the mesylate (**5**) by treating the latter with lithium bromide. Bromide (**7**) gave the corresponding cyanide (**9**) by reaction with sodium cyanide in DMSO. Saponification of **9** by refluxing with potassium hydroxide in ethylene glycol led to (*Z*)-5-dodecenoic acid, characterised and identified through its methyl ester (**11**). Lithium aluminium hydride reduction of **11** gave (*Z*)-5-dodecen-1-ol (**13**) which on acetylation gave **1**.

By an analogous sequence of reactions the (*Z*)-4-tri-decenol was converted into **2**.



(1) n = 4 (2) n = 6

(3) n = 4 R = OH (4) n = 6 R = OH

(5) n = 4 R = O—S(=O)(=O)—CH$_3$ (6) n = 6 R = O—S(=O)(=O)—CH$_3$

(7) n = 4 R = Br (8) n = 6 R = Br

(9) n = 4 R = CN (10) n = 6 R = CN

(11) n = 4 R = COOCH$_3$ (12) n = 6 R = COOCH$_3$

(13) n = 4 R = CH$_2$OH (14) n = 6 R = CH$_2$OH

Experimental

1-*Bromo*-(*Z*)-4-*undecene* (**7**) *and* 1-*bromo*-(*Z*)-4-*tridecen* (**8**)

A solution of **3** (6.35 g; 0.037 mole) and triethylamine (11.31 g; 0.11 mole) in dichloromethane (50 ml) was stirred with methanesulphonyl chloride (5.13 g; 0.044 mole) at 0° for 0.5 hr and then at room temperature for 6 hr. Dichloromethane was distilled and the residue diluted with water, extracted with ether (3 × 50 ml), the ether layer washed with water, dried and solvent removed to give the mesylate (**5**).

Mesylate (**5**) was stirred with lithium bromide (5.6 g; 0.064 mole) in dry acetone (100 ml) for 5 hr at room temperature. Acetone was distilled under reduced pressure, the residue extracted with ether, the ether layer washed with water, brine, dried and distilled to afford a liquid which was purified by column chromatography over silica gel to give pure bromide (**7**) (7.2 g; 96%); ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, distorted t), 1.1-1.53 (10H, bm), 1.72-2.43 (4H, m), 3.36 (2H, t, J = 6 Hz), 5.1-5.67 (2H, m) (Found: C, 56.3; H, 9.3; Br, 33.9. $C_{11}H_{21}Br$ requires C, 56.7; H, 9.1; Br, 34.3%).

Similarly 1-bromo-(*Z*)-4-tridecene (**8**) was obtained in 86% yield; ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, distorted t), 1.2 (12H, bs), 1.65-2.35 (6H, m), 3.35 (2H, t, J = 6 Hz), 5.05-5.55 (2H, m) (Found: C, 59.4; H, 9.4; Br, 30.3. $C_{13}H_{25}Br$ requires C, 59.8; H, 9.6; Br 30.6%).

1-*Cyano*-(*Z*)-4-*undecen* (**9**) *and* 1-*cyano*-(*Z*)-4-*tridecen* (**10**)

A mixture of **7** (2.5 g; 0.01 mole) and sodium cyanide (0.735 g; 0.015 mole) in DMSO (15 ml) was stirred overnight at room temperature. The reaction mixture was diluted with water, extracted with ether, the organic extract washed with water, brine, dried and solvent removed by distillation. Column chromatography of the crude product using silica gel gave the pure **9** (1.4 g; 73%); IR: 2240 cm^{-1} (C≡N);

† NCL Communication No. 4474

^{1}HNMR ($CDCl_3$): δ 0.88 (3H, distorted t), 1.0-1.45 (8H, bs), 1.55-2.4 (8H, m), 5.0-5.6 (2H, m); MS: m/z 179 (M^+) (Found: C, 80.0; H, 12.0; N, 8.1. $C_{12}H_{21}N$ requires C, 80.4; H, 11.8; N, 7.8%).

Similarly compound (**10**) was obtained from **8** in 86% yield; IR: 2235 cm^{-1} (C ≡ N) (Found: C, 81.4; H, 12.4; N, 7.1. $C_{14}H_{25}N$ requires C, 81.1; H, 12.2; N, 6.8%).

Methyl (Z)-5-dodecenoate (**11**) *and methyl (Z)-5-tetra-decenoate* (**12**)

Compound **9** (1.4 g; 0.0078 mole) and KOH (1.31 g; 0.023 mole) were refluxed in ethylene glycol for 6 hr. Usual work up gave the acid which was esterified with diazomethane. The pure methyl ester (**11**) (1.3 g; 93%) was obtained by column chromatography using silica gel (Found: C, 73.2; H, 11.2. $C_{13}H_{24}O_2$ requires C, 73.5; H, 11.4%)

Similarly, methyl (*Z*)-5-tetradecenoate (**12**) was obtained in 92% yield (Found: C, 75.1; H, 11.6. $C_{15}H_{28}O_2$ requires C, 75.0; H, 11.9%).

(*Z*)-5-*Dodecen*-1-*ol* (**13**) *and* (*Z*)-5-*tetradecen*-1-*ol* (**14**)

Methyl ester **11** (0.532 g; 0.0025 mole) in dry ether (20 ml) was added dropwise to the suspension of lithium aluminium hydride (0.190 g; 0.005 mole) in ether (20 ml) at 0° under stirring. After the addition was over, stirring was continued for 3 hr more at room temperature. Usual work up gave the aclohol (**13**) which was purified by column chromatography using silica gel; IR: 3340 cm^{-1} (−OH); ^{1}HNMR ($CDCl_3$): δ 0.88 (3H, distorted t), 1.11-1.80 (12H, bm), 1.44 (1H, D_2O exchangeable), 1.84-2.42 (4H, m), 3.66 (2H, t, J = 6 Hz), 5.20-5.60 (2H, m); MS: m/z 184 (M^+). (Found: C, 78.5; H, 13.3. $C_{12}H_{24}O$ requires C, 78.2; H, 13.1%).

Similarly (*Z*)-5-tetradecen-1-ol (**14**) was obtained from (**12**) in 90% yield (Found: C, 78.8; H, 13.5. $C_{14}H_{28}O$ requires C, 79.2; H, 13.3%).

(*Z*)-5-*Dodecenyl acetate* (**1**) *and* (*Z*)-5-*tetradecenyl acetate* (**2**)

The alcohol **13** (0.466 g; 0.0025 mole) in pyridine (1 ml) was treated with acetic anhydride (0.516 g; 0.005 mole) at room temperature for 24 hr. Work up and column chromatogrpahy using silica gel gave the pure **1** (0.529 g; 96%); IR: 1740 cm^{-1} ($OCOCH_3$); ^{1}H NMR ($CDCl_3$): 0.88 (3H, distorted t), 1.13-1.86 (12H, bm), 2.04 (7H, singlet overlapping a mutiplet), 4.06 (2H, t, J = 6 Hz), 5.17-5.58 (2H, m); MS: m/z 226 (M^+). (Found: C, 74.1; H, 11.4. $C_{14}H_{26}O_2$ requires C, 74.3; H, 11.6%).

Similarly (*Z*)-5-tetradecenyl acetate (**2**) was obtained in 74% yield: IR: 1740 cm^{-1} ($OCOCH_3$); ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, distorted t), 1.05-1.75 (16H, bm), 2.0 (7H, singlet overlapping a multiplet), 4.0 (2H, t, J = 6 Hz), 5.16-5.4 (2H, m); MS: m/z 254 M^+ (Found: C, 77.63; H, 11.65. $C_{16}H_{30}O_2$ requires C, 77.5; H, 11.9%).

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Symposide: A new anti-fibrinolytic glycoside from *Symplocos racemosa* Roxb.†

Rashmi Dhaon, G K Jain, J P S Sarin & N M Khanna*
Central Drug Research Institute, Lucknow 226 001

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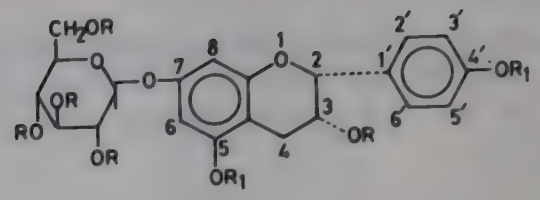
Symposide, a new flavan-glycoside showing anti-fibrinolytic activity, isolated from the stem bark of *Symplocos racemosa* Roxb. was characterized as (−)-epiafzelechin-7-β-D-glucopyranoside.

In indigenous system of medicine, *Symplocos racemosa* Roxb,[1] (Lodh), is used for managenemt of menstrual disorders and to provide firmness to spongy and bleeding gums. Its decoction is also used for the treatment of bowel complaints and ulcers.

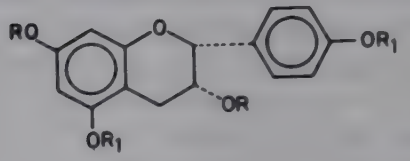
In a project of screening Indian plants over a wide range of biological activities, we found that a 95% ethanolic extract of this plant showed anti-fibrinolytic activity. Systematic solvent fractionation of the concentrate from ehtanolic extract localized the activity in *n*-butanol soluble fraction which on column chromatography yielded α-amyrin[2], β-sitosterol[3], (−)-epiafzelechin[4] and a new flavanglycoside (**1**) named as symposide. Of these (−)-epiafzelechin and symposide were found to possess anti-fibrinolytic activity when tested *in-vitro* on fibrin plates against urokinase and were also effective in preventing excessive menstrual blood loss in monkeys fitted with intra uterine contraceptive devices (IUCDs).

Symposide (**1**) gave negative Wilson boric acid test[5] and intense red colour with conc. H_2SO_4 for flavans. On heating with vanillin-HCl it produced a brick red colour indicating a phloroglucinol moiety in the molecule. A faint green colour with alc. $FeCl_3$ showed the presence of free phenolic OH, particularly at C-5. Positive Feigl test[6] suggested it to be a glycoside.

Its IR spectrum showed absorptions at 3400 (OH) and 1080 cm^{-1} (C−O−C glycosidic linkage). Its PMR spectrum displayed signals at δ 2.70 (bd, $W_{\frac{1}{2}}$ = 9 Hz, 2H, 4-CH_2), 4.23 (bs, 3-H), 4.82 (bs, 2-H), 5.92 (1H, d, J = 2 Hz, 8-H), 6.14 (1H, d, J = 2 Hz, 6-*H*), 6.74 and 7.28 (AA′BB′ system, J = 9 Hz for ortho-ortho coupling and J = 2 Hz for meta-meta coupling, 2′,6′-H and 3′,5′-*H* respectively), FD



1. R, R_1=H
2. R, R_1=Ac
4. R=H; R_1=Me



3. R = R_1=H
5. R = H, R_1=Me
6. R = Ac, R_1=Me

mass spectrum of **1** showed M^+ at m/z 436 and a prominent ion peak at m/z 274 (M-162) which indicated the presence of one hexose moiety in the molecule. This was confirmed by the mass spectrum of symposide peracetate (**2**) which showed prominent ions at m/z 331, 271, 211, 169, 149 and 109 due to tetraacetylated hexose moiety[7]. Symposide when hydrolysed with β-glucosidase yielded D-glucose and an aglycone (**3**) indicating β-linkage of the glucose in it. A comparison of IR, PMR and mass spectrum and other diagnostic colour reactions indicated the aglycone to be (−)-epiafzelechin[4] (**3**).

Symposide formed a dimethyl ether (**4**) which on enzymatic cleavage with β-glucosidase gave aglycone dimethyl ether (**5**) and the latter on acetylation formed a diacetate (**6**). Mass spectrum of **6** showed retro-Diels-Alder fragments at m/z 195 ($C_{10}H_{11}O_4$) and at m/z 191 ($C_{11}H_{11}O_3$) indicating that glucose was attached to ring-A in symposide either at C-5 or C-7 position. These two possibilities could be distinguished by comparison of the PMR spectrum of **5** and **6** wherein proton at C-6 appeared at δ 6.05 and 6.35 respectively and the proton at C-8 appeared at δ 5.89 and 6.22 respectively. A symmetric downfield shift of 0.3 to 0.33 ppm for H-6 and H-8 protons in **6** confirmed the presence of acetyl function of C-7 thereby suggesting that glucose was linked to aglycone through C-7 OH in symposide. Based on the data gathered, symposide could be characterized as cis-2-(4′-hydroxyphenyl)-3,4-dihydro-3,5-dihydroxy-2*H*-[1]-benzopyran-7-yl-β-D-glucopyranoside (**1**).

†CDRI communication No. 4394

An interesting offshoot of this work was that, thatcatechin was also found to exhibit anti-fibrinolytic activity activity thereby highlighting the association of this activity with such molecular framework.

Experimental

Extraction and isolation of compounds

Air-dried, finely powdered stem bark (1.3 kg) of *Symplocos racemosa* Roxb. was exhaustively percolated with 95% ethanol (2 litre × 7) at room temperature. The combined extracts were concentrated under reduced pressure below 45° and the residual dark brown solid (~ 180 g) was successively fractionated with benzene (500 ml × 3), chloroform (500 ml × 5) and *n*-butanol (500 ml × 5). The *n*-butanol soluble fraction was concentrated and dried under reduced pressure below 45° to give a dark reddish brown solid (~ 80 g). A portion (40 g) of this solid was subjected to column chromatography over silica gel (1 kg) using EtOAc (eluate Nos 1 to 9, 300 ml each), EtOAc-MeOH (98 : 2, eluate Nos. 10-55, 350 ml each), EtOAc-MeOH (95 : 5, eluate Nos. 56-65, 300 ml each) and EtOAc-MeOH (75 : 25, eluate Nos. 66-95, 300 ml each).

Eluate Nos. 4-9 provided a green viscous mass (3 g; fraction-A) and eluate Nos. 29-42 gave a cream-coloured semi-crystalline solid (4.5 g; fraction-B). Fraction-A was rechromatographed over silica gel (100 g) using chloroform and chloroform-methanol (9 : 1) as the eluent. Elution with chloroform yielded α-amyrin (75 mg) and β-sitosterol (120 mg) while elution with $CHCl_3$-MeOH (9 : 1) provided (−)-epiafzelechin (**3**, 180 mg). Fraction-B was almost pure and crystallized from EtOAc-MeOH (1 : 1) to give symposide (**1**) as flat needle shaped crystals, m.p. 192-95°, $[\alpha]_D^{20} - 58.65$; R_f 0.55, (TLC, silica gel G plates, $CHCl_3$-MeOH, 8 : 2, detection with 0.1% Aq. $KMnO_4$); UV (MeOH): 230, 275 nm (Found: C, 57.8; H, 5.6. $C_{21}H_{24}O_{10}$ requires C, 57.8; H, 5.5%).

Symposide peracetate (**2**) was prepared as usual (Py/Ac_2O, 1 ml each; 24 hr at room temp.). It was obtained as white amorphous solid, m.p. 170-73°; PMR ($CDCl_3$): δ 1.82, 1.84, 1.90, 1.98, 2.02, 2.18, 2.22 (all s, 7 × $OCOCH_3$), 2.78 (bd, $W_{\frac{1}{2}} = 9$ Hz, 4-CH_2), 5.02 (bs, 2-*H*), 5.20 (bs, 3-H), 6.34 (d, J = 2 Hz, 6-H), 6.48 (d, J = 2 Hz, 8-H), 7.02-7.42 (dd, J = 9 Hz ortho-ortho, J = 2 Hz meta-meta, 2′-6′ and 3′-5′-H); MS: m/z 730 (M^+) (Found: C, 57.6; H, 5.2. $C_{35}H_{38}O_{17}$ requires C, 67.5; H, 5.2%).

(−)-Epiafzelechin (**3**): To a solution of symposide (200 mg) in water (5 ml) was added β-glucosidase (200 mg) and 2-3 drops of xylene. The reaction mixture was stirred at room temperature for 72 hr followed by extraction with EtOAc (10 ml × 5). The combined extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give **3** as a cream coloured crystalline solid (90 mg), m.p., m.m.p. 215-18°; $[\alpha]_D^{20} - 57.06$ ($CHCl_3$) (Found: C, 65.7; H, 5.1. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%).

Symposide dimethyl ether (**4**): Symposide (200 mg) was dissolved in Ether-MeOH (1 : 1, 10 ml) and methylated with ethereal diazomethane under ice cooling and kept overnight at 0°C. Usual work-up yielded **4** as a light cream coloured crystalline solid (200 mg), m.p. 143-45° (Found: C, 59.5; H, 6.1%. $C_{23}H_{28}O_{10}$ requires C, 59.5; H, 6.0%); R_f 0.5 (TLC, silica-gel G plates, $CHCl_3$-MeOH 17 :3, detection with 0.1% aq. $KMnO_4$); IR (KBr): 3360 (OH), 2900 (C−H stretchings), 1080-1100 cm^{-1} (glycosidic ether linkage); PMR ($CDCl_3$): δ 2.80 (br d, $W_{\frac{1}{2}}$ 9 Hz, 4-CH_2), 3.68 (s, 1 × OCH_3), 3.72 (s, 1 × OCH_3), 4.28 (br s, 3-*H*), 4.82 (br s, 2-*H*), 6.14 (d, J = 2 Hz, 8-*H*), 6.24 (d, J = 2 Hz, 6-*H*), 6.82 (d, J = 9 Hz ortho-ortho and J = 2 Hz meta-meta coupling, 2′,6′-*H*), 7.38 (d, J = 9 Hz ortho-ortho and J = 2 Hz meta-meta coupling, 3′, 5′-H); MS: M^+ 464

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A new binaphthoquinone from *Plumbago zeylanica* Linn.

B Dinda* & (Miss) S Saha
Department of Chemistry, Tripura University, Agartala 799 004

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A new binaphthoquinone designated as chitanone has been isolated from the aerial parts of *Plumbago zeylanica* Linn. Based on spectral and chemical studies, it has been assigned the stereostructure as 1,2-dihydro-1(*S*),5,5′-trihydroxy-2′,3(*R*)-dimethyl-2(*R*)-propyl-3,8′--binaphthalene-1′,4,4′-trione (I).

Recent studies[1,2] on the medicinal plant, *Plumbago zeylanica* Linn. (Bengali: Chita), (fam. Plumbaginaceae) have resulted in the identification of several naphthoquinones, amino acids, flavonoids and β-sitosterol. The petrol extract of the aerial parts of its plant was reinvestigated and a new quinone, designated as chitanone was isolated. The spectral and chemical evidences leading to structure (I) for chitanone are reported herein.

Chitanone, $C_{25}H_{24}O_6$ (M^+ 420), exhibited in its UV spectrum in MeOH λ_{max} at 212 (log ε, 4.62), 261 (4.22), 334 (3.72) and 415 (3.51), while its IR spectrum in KBr exhibited characteristic absorptions at 3500-3300 (OH), 1705, 1660 and 1645 (unchelated and chelated >C=O), 1610 (>C=C< cm^{-1}, which correspond[3,4] to a combination of those of plumbagin and its hydrogenated derivative. Its ^1H NMR spectrum ($CDCl_3$, 100 MHz, δ) displayed signals for two alkyl methyl groups (0.86, distorted t, 1.40, s), two methylene groups (1.26-1.68, m), one alcoholic hydroxyl group (1.98, d, J = 1.5 Hz, exchangeable with D_2O), one vinylic methyl group (2.20, d, J = 1.5 Hz), two methine protons (2.44, m; 4.62, d, J = 10 Hz), one vinylic proton (6.80, q, J = 1.5 Hz), five aromatic protons (7.14-7.32, 2H, m; 7.52-7.66, 3H, m) and two phenolic *peri*-hydroxyl groups (11.94, s, exchangeable with D_2O). These data suggested[3] the presence of both plumbagin and its tetrahydro analogue unit in the molecule. The EI mass spectrum of chitanone was diagnostic and established its skeletal structure. The spectrum revealed some significant intense mass peaks at m/z (420 (M^+) (11.9%), 405 ($M-CH_3$)$^+$ (4.2), 313 (4.2), 233 (3.32), 232 (8.3), 218 (18.3), 205 (40.0), 203 (11.7), 188 (100.0), 160 (96.7), 149 (85.0), 145 (22.1), 132 (82.3), 131 (96.9), 120 (92.1), 92 (77.7) and 63 (54.2) which can be rationalised[5,6] (see Scheme 1) by considering structure (I) for it.

The dimethyl ether of chitanone ($C_{27}H_{28}O_6$; M^+ 448) was obtained as an amorphous solid, m.p. 122°. ^1H NMR spectrum ($CDCl_3$, 100 MHz) of this derivative was similar to that of its parent compound except for two *peri*-hydroxyl groups which disappeared and two methoxyl signals appeared at δ 3.98 (6H, s). As the two methoxyls appeared in the same region and probably have the same electronic environment and hence a 3,8′-linkage between two monomeric naphthoquinone units in chitanone was considered likely by analogy with neodiospyrin dimethyl ether (II)[7], where the two methoxyls appeared almost in the same region. Therefore, chitanone was 1,2-dihydro-1,5,5′-trihydroxy-2′,3-dimethyl-2-propyl-3,8′-binaphthalene-1′, 4, 4′-trione (I).

It remained then to determine the stereochemical assignment of groups at C-1, C-2 and C-3. The coupling constant of H-1 with H-2 is 10 Hz suggesting that these hydrogens are *trans* to each other. Furthermore, a comparison of CD spectra (Fig. 1) of chitanone with isoshinanolone (IIIA) and 1,2(3)-tetrahydro-3,3′-biplumbagin (IIIB) of known absolute configuration at C-1 (as *R*)[3,8] suggested *S*-

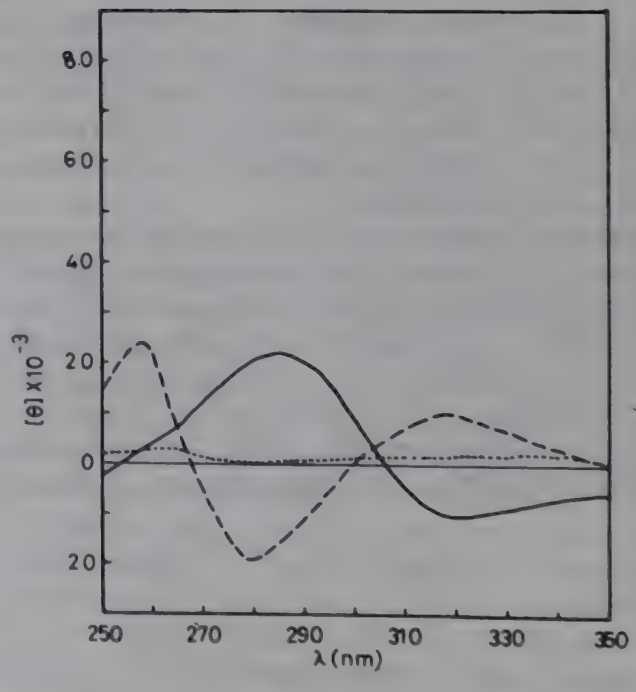
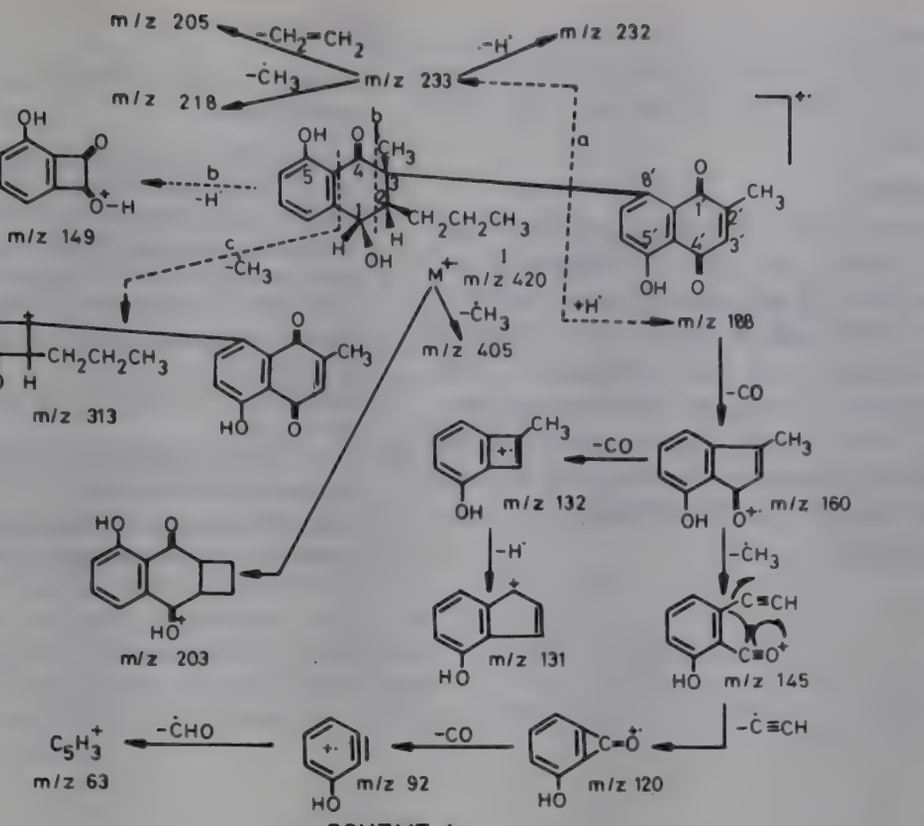
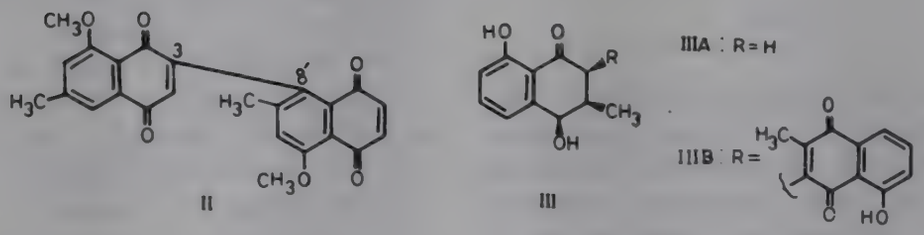


Fig. 1—CD spectra of chitanone (I) (—), isoshinanolone (IIIA) (.....) and 1,2(3)-tetrahydro-3,3′-biplumbagin (IIIB) (-----)



SCHEME 1



configuration at C-1 in chitanone. Thus the relative stereochemical arrangement of groups at C-2 was considered as *R*. The configuration at C-3 was assigned as *R* by assuming the *cis*-relationship between H-2 and CH_3-3 as loss of methane was not observed in the mass spectrum of the compound. Therefore, the quinone was assigned the stereostructure as 1,2-dihydro-1(*S*),5,5′-trihydroxy-2′,3(*R*)-dimethyl-2*R*-propyl-3,8′-binaphthalene-1′,4,4′-trione (I). It requires final confirmation by a few more chemical reactions and X-ray analysis.

Interestingly, this appears to be the first report of the occurrence of a naphthoquinone having a propyl group. Moreover, cooccurrence of chitanone and 1,2(3)-tetrahydro-3,3′-biplumbagin in the same plant with opposite CD curve is significant from biogenesis view point.

Experimental

Aerial parts of *P. zeylanica* collected from West Bengal were exhaustively extracted with petrol (60-80°) and the petrol extract was concentrated and column chromatographed over silica gel (60-120 mesh) column with petrol, petrol-benzene mixtures, benzene and benzene-chloroform mixtures. Petrol-benzene (4:1) eluate yielded a residue which on repeated column chromatography afforded chitanone as bright orange crystalline solid, m.p. 90° (yield, 0.0003%).

Methylation of chitanone

Chitanone (0.015 g) in $CHCl_3$ (10 ml) was refluxed with CH_3I (2 ml) and Ag_2O (0.03 g) for 18 hr. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was column chromatographed over silica gel when a pure yellow amorphous solid of dimethyl ether of chitanone (0.009 g), m.p. 122° was obtained from petrol-benzene (6:1) eluate, $C_{27}H_{28}O_6$ (M^+ 448); ^1H NMR ($CDCl_3$, 100 MHz, δ): 0.85 (3H, t, Me), 1.40 (3H, s, Me), 1.24-1.70 (4H, m, $2CH_2$), 1.96 (1H, d, J = 1.5 Hz, exchangeable with D_2O; OH), 2.20 (3H, d,

J = 1.5 Hz, Me-2'), 2.45 (1H, m, H-2), 3.98 (6H, s, 2 OMe), 4.64 (1H, d, J = 10 Hz, H-1), 6.80 (1H, q, J = 1.5 Hz, H-3'), 7.20-7.40 (2H, m, Ar − H), 7.58-7.76 (3H, m, Ar − H).

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The authors thank Dr S C Pakrashi and Dr P Dastidar (IICB, Calcutta), and Dr D S Bhakuni (RSIC, Lucknow) for ^{1}H NMR and mass spectra; Prof. U R Ghatak and Dr S P Bhattacharyya (IACS, Calcutta) for IR and CD spectra and Prof. K M Biswas (Calcutta University) for UV spectra. The plant product was procured from United Chemical and Allied Products, Calcutta. One of the authors (SS) is grateful to the CSIR, New Delhi for the award of a senior research fellowship.

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Synthesis and biological activity of 3,6-diaryl-1,2,4-triazolo[3,4-*a*]-phthalazines†

Mehboob Razvi*, T Ramalingam & P B Sattur
Regional Research Laboratory, Hyderabad 500 007

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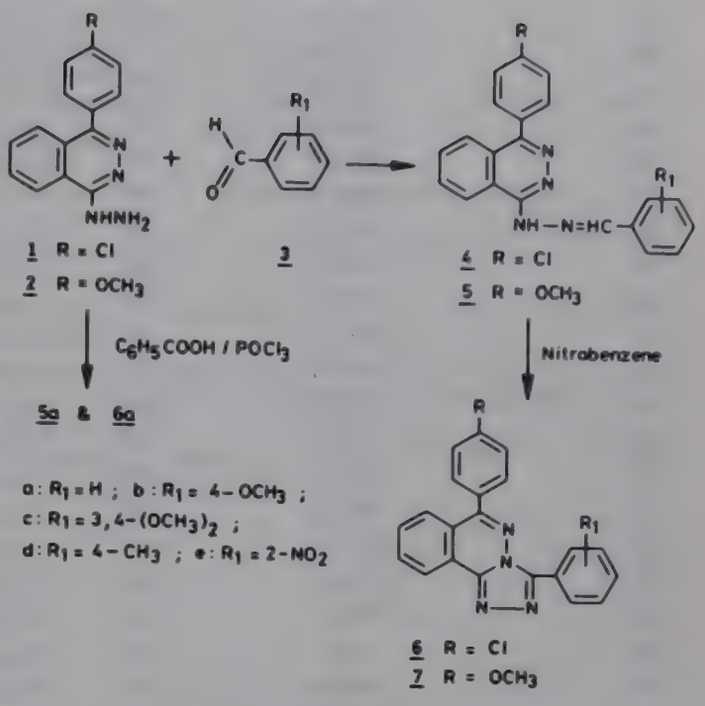
4-(4′-Chlorophenyl)-1-hydrazinophthalazine (**1**) and 4-(4′-methoxyphenyl)-1-hydrazinophthalazine (**2**) condense with aromatic aldehydes (**3**) to give 4-(4′-chlorophenyl)-1-benzalhydrazinophthalazines (**4**) and 4-(4′-methoxyphenyl)-1-benzalhydrazinophthalazines (**5**), respectively which on oxidative cyclization afford the corresponding 3,6-diaryl-1,2,4-triazolo[3,4-*a*]phthalazines (**6** and **7**). The compounds (**6** and **7**) have been screened for their analgesic, antiinflammatory, motor and antihypertensive activities.

Litwin *et al.*[1] have reported that 1-hydrazinophthalazine (hydralazine), an antihypertensive drug, is converted to 3-methyl-1,2,4-triazolo[3,4-*a*]phthalazine in the body. 1,2,4-Triazole derivatives[2,3] are of interest due to their biological importance as drugs and pesticides. These findings prompted us to synthesise[4] and evaluate the biological activities of various 1-benzalhydrazino-4-phenyl/tolyl-phthalazines and 3-aryl-6-phenyl/tolyl-1,2,4-triazolo[3,4-*a*]phthalazines. With a view to studying the effect of chloro and methoxy substituents at 6-phenyl ring of 3,6-diaryl-1,2,4-triazolo[3,4-*a*]phthalazines and in continuation of our incessant efforts to obtain useful biologically active molecules[4-6], which may emerge as drugs, we report herein the synthesis and biological activities of 3-aryl-6-(4′-chlorophenyl)-1,2,4-triazolo[3,4-*a*]phthalazines (**6**) and 3-aryl-6-(4′-methoxyphenyl)-1,2,4-triazolo[3,4-*a*]phthalazines (**7**).

The synthesis of **6** and **7** (Scheme 1) was accomplished in 70-90% yields by oxidative cyclization of **4** and **5** respectively employing nitrobenzene as oxidising agent. In another route, **6a** and **7a** were obtained in a single step in 68-70% yield, by the reaction of 4-chlorophenyl-1-hydrazinophthalazine (**1**) and 4-methoxyphenyl-1-hydrazinophthalazine (**2**) respectively with benzoic acid in the presence of $POCl_3$. Compounds **4** and **5** in turn were prepared in 70-85% yields by condensing **1** and **2** respectively with aromatic aldehydes (**3**).



Scheme 1

The required phthalazines (**1** and **2**) were prepared from the corresponding 4-aryl-1-chlorophthalazines[7] following the literature method[8]. The structural assignments of all the compounds prepared are based on elemental analyses, IR and mass spectral data. The characterization data of the compounds **4-7** are given in Table 1.

Compounds **4** and **5** showed bands at 3310(NH), 1660(N=CH) and 1580 cm^{-1} (aromatic stretching) while their cyclic derivatives (**6** and **7**) exhibited bands at 1640(N=C) and 1580 cm^{-1} (aromatic stretching) in their IR spectra. Mass spectra of the comounds **6** and **7** were in confirmity with their structures.

Biological activity

Analgesic, antiinflammatory, motor and antihypertensive activities of the compounds **6** and **7** were determined by literature methods[9-11]. Compounds **6d** and **6e** exhibited promising antiinflammatory activity (40 and 45% respectively) in rats while phenylbutazone at the same dose (100 mg/kg, p.o.) produced 40% inhibition of 1% carrageenin-induced edema. The compounds showed mild analgesic activity (4-28%) in comparison to aspirin (60%) at 100 mg/kg. The results of spontaneous motor activity revealed that **6b, 6c, 6d, 6e** and **7c** cause 57-75% decrease in motor activity (Table 2)

†RRL(H) Communication No.2342

Table 1—Characterization data of compounds **4-7**

Compd	m.p. °C	Yield (%)	Mol. formula	N (%) Found	N (%) Calc.
4a	168-70	85	$C_{21}H_{15}N_4Cl$	15.4	15.6
4b	215-16	72	$C_{22}H_{17}N_4ClO$	14.2	14.4
4c	200-01	75	$C_{23}H_{19}N_4ClO_2$	13.4	13.4
4d	165-67	76	$C_{22}H_{17}N_4Cl$	15.1	15.0
4e	200-02	80	$C_{21}H_{14}N_5ClO_2$	19.4	19.5
5a	148-50	80	$C_{22}H_{18}N_4O$	15.6	15.8
5b	181-82	85	$C_{22}H_{14}N_4O_2$	15.0	15.0
5c	185-87	75	$C_{23}H_{21}N_4O_3$	14.2	14.1
5d	172-73	72	$C_{23}H_{20}N_4O_2$	14.6	14.6
5e	175-77	70	$C_{22}H_{18}N_5O_3$	14.0	14.0
6a	268-70	87	$C_{21}H_{13}N_4Cl$	15.9	15.7
6b	>350	88	$C_{22}H_{15}N_4ClO$	14.4	14.5
6c	292	90	$C_{23}H_{17}N_4ClO_2$	13.3	13.4
6d	278-79	80	$C_{22}H_{15}N_4ClO$	15.3	15.1
6e	260-61	82	$C_{21}H_{12}N_5ClO_2$	17.5	17.4
7a	225-26	80	$C_{22}H_{16}N_4O$	15.7	15.9
7b	258-59	81	$C_{23}H_{18}N_4O_2$	14.8	14.7
7c	279-81	72	$C_{24}H_{20}N_4O_3$	13.5	13.6
7d	236	70	$C_{23}H_{18}N_4O$	15.3	15.3
7e	260-61	80	$C_{22}H_{15}N_5O_3$	17.5	17.6

Table 2—Biological screening results of the compounds **6** and **7**

Compd	% Decrease in motor activity at 100 mg/kg (i.p. mice)	Analgesic activity at 100 mg/kg (% protection of pain)	Antiinflammatory activity at 100 mg/kg (% inhibition)
6a	49	10	27
6b	61	10	27
6c	57	15	31
6d	57	28	40
6e	75	7	35
7a	5	8	27
7b	34	4	18
7c	57	5	18
7d	22	6	8
7e	41	7	17

with mild sedation. Antihypertensive activity of compounds was determined at a dose of 5 mg/kg i.v. and the results as decrease in blood pressure (mm Hg) were calculated. It was found that compounds **6** and **7** showed mild and insignificant fall in blood pressure (10-15 mm Hg) whereas hydralazine at 2 mg/kg i.v. produced a gradual and transient fall (42 mm Hg) in blood pressure for a long duration.

Experimental

Melting points were taken in open capillaries on a Buchi 510 melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra on a Hitachi RMU 6L mass spectrometer at 70 eV.

4-Aryl-1-benzalhydrazinophthalazines (*4a-e and 5a-e*)

A mixture of **1** (0.05 mole) and aromatic aldehyde (**3**; 0.05 mole) in ethanol (250 ml) was heated under reflux for 2 hr and cooled. The product, thus separated, was filtered, washed with ether and recrystallized from ethanol to give **3** or **4** (Table 1) in 70-85% yields.

3-Phenyl-6-(4'-methoxyphenyl)-1,2,4-triazolo[3,4-a]phthalazine (**7a**)

Method 1—A mixture of **5a** (3.9 g; 0.011 mole) and nitrobenzene (35 ml) was refluxed in an oil-bath for 4 hr. Nitrobenzene was removed by steam distillation, the crude product washed with pet. ether and recrystallized from acetic acid to give **7a**, m.p.225-26°; MS;m/z 352(M^+), 351(M^+-H), 324(M^+-N_2), 275($M^+-C_6H_5$), 259($M^+-C_7H_5N$), 245($M^+-C_7H_7O$), 223($M^+-C_8H_5N_2$), 195($M^+-C_8H_5N_4$), 142($M^+-C_{14}H_{12}NO$) and 88($M^+-C_{15}H_{12}N_4O$).

Compounds **6a-e** and **7b-e** (Table 1) were prepared and identified similarly.

Method 2—A mixture of 4-methoxyphenyl-1-hydrazinophthalazine (**2**, 0.01 mole), benzoic acid (0.011 mole) and $POCl_3$ (8 ml) was refluxed for 4 hr. After cooling, it was poured into crushed ice to give a solid product which on washing with a dil. solution of $KHCO_3$ followed by water and recrystallization from acetic acid gave **7a**, yield 70%, m.p. 225-26°, identical in all respects with that obtained by method 1.

Compound **6a** was prepared in the same way in 68% yield and was found to be similar in all respects with **6a** obtained by cyclization of **4a** with nitrobenzene employing method 1.

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Synthesis and antiparkinsonian activity of newer imidazolones

Pankaj K Naithani, Vijai K Srivastava, J P Barthwal, Anil K Saxena, T K Gupta & K Shanker*

Jawahar Lal Nehru Laboratory of Molecular Biology, Department of Pharmacology & Therapeutics, King George's Medical College, Lucknow 226 003

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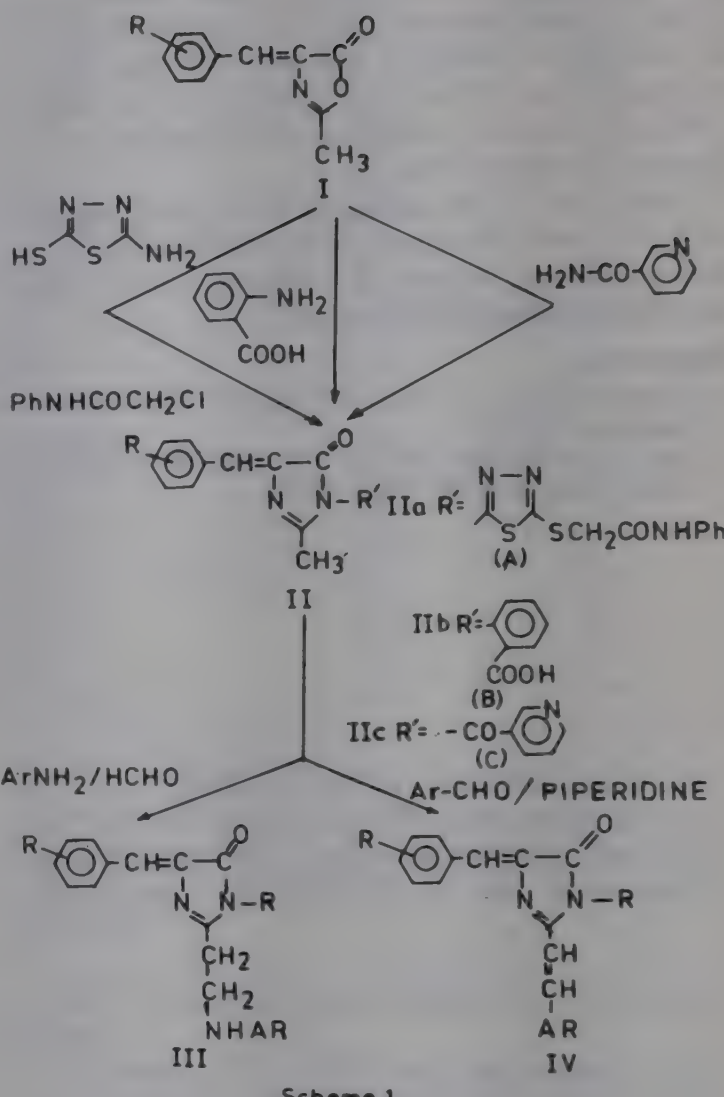
2-[5-(4-Arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilides (IIa), *o*-(4-arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)benzoic acids (IIb) and 4-benzylidene-2-methyl-1-nicotinoyl-2-imidazolin-5-one (IIc) have been prepared from 4-arylidene-2-methyl-5-(4*H*)oxazolones (I) using 5-amino-2-mercapto-1,3,4-thiadiazole and α-chloroacetanilides, anthranilic acid, and nicotinamide respectively, and converted into various mannich bases (III) and styryl derivatives (IV). Compounds IIIa-k and IVa-i have been evaluated for their antiparkinsonian activity.

Heterocycles having two nitrogen atoms oriented at 1,3-positions in the ring show potent antiparkinsonian activity[1-5]. It was therefore thought desirable to synthesize imidazolones and study their antiparkinsonian activity.

The intermediate 4-arylidene-2-methyl-5(4*H*)-oxazolones (I) were prepared by condensation of arylaldehydes with acetylglycine in the presence of sodium acetate and acetic anhydride. These oxazolones were converted into 2-[5-(4-arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilides (IIa) using 5-amino-2-mercapto-1,3,4-thiadiazole and α-chloroacetanilide, *o*-(4-arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)benzoic acids (IIb) using anthranilic acid and 4-benzylidene-2-methyl-1-nicotinoyl-2-imidazolin-5-one (IIc) using nicotinamide. The IR spectra of IIa exhibited characteristic bands at 1670 (C=O function in a five-membered ring) and 1520 cm^{-1} (C=N). The mass spectrum of *o*-(4-benzylidene-2-methyl-5-oxo-2-imidazolin-1-yl)benzoic acid (IIb_1) exhibited the molecular ion peak at m/z 306 and the base peak at m/z 105.

The imidazolones II were treated with arylamines and formaldehyde in ethanol to give the mannich bases (III). The PMR spectrum of 2-{5-[4-benzylidene-5-oxo-2-(2-*m*-toludinoethyl)-2-imidazolin-1-yl]-1,3,4-thiadiazol-2-ylthio}acetanilide (IIIf) showed signals at δ 7.05-8.3 (m, 14H, Ar−H), 5.1-6.1 (br, 2H, 2×NH) 3.4-3.6 (m, 1H, CH), 3.0-3.4 (d, 6H, 3×CH_2) and 1.5-1.7 (s, 3H, CH_3).



Scheme 1

Condensation of II with aryl aldehydes in the presence of piperidine yielded 2-{5-[4-arylidene-5-oxo-2-(substituted styryl)-2-imidazolin-1-yl]1,3,4-thiadiazol-2-ylthio}-acetanilides, *o*-[4-arylidene-5-oxo-2-(substituted styryl)-2-imidazolin-1-yl]benzoic acids or 4-arylidene-1-nicotinoyl-2-(substituted styryl)-2-imidazolin-5-ones (IV) (Scheme 1). The mass spectrum of 4-benzylidene-2-(2-hydroxystyryl)-1-nicotinoyl-2-imidazolin-5-one (IVi) exhibited the molecular ion peak at m/z 395 and the base peak at m/z 43.

Biological activity

The mannich bases (IIIa-k) and styryl derivatives (IVa-i) were evaluated for their antiparkinsonian activity according to our earlier method[3].

Compound IIIg exhibited potent antiparkinsonian activity with a high ALD_{50} value.

Experimental

Melting points were taken in open capillary tubes and are uncorrected. Compounds were routinely checked for their purity by TLC on silica gel G. IR spectra were recorded in KBr on a Perkin-Elmer 157 infracord spectrometer (ν_{max} in cm^{-1}), mass spectra on a JMSD 300 instrument fitted with JMS 2000 data system at 70 eV, and PMR spectra on a Varion A 60D instrument (chemical shift in δ, ppm). Characterization data of III and IV are given in Table 1.

2-[5-(4-Arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilides (IIa), o-(4-arylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-benzoic acids (IIb) and 4-benzylidene-2-methyl-1-nicotinoyl-2-imidazolin-5-one (IIc)

A mixture of I (0.01 mole) and 5-amino-2-mercapto-1,3,4-thiadiazole (0.01 mole) was fused on a sooty flame till no more water separated from the reaction mixture. The solid thus obtained was cooled, washed with water and recrystallized. An equimolear mixture of this product and α-chloroacetanilide in benzene containing triethylamine was refluxed for 8 hr. The solvent was removed and the residue suspended in ice cold water. The solid thus separated was washed with water and recrystallized to give IIa.

Similarly, a mixture of I (0.01 mole) and anthranilic acid or nicotinamide (0.01 mole) was fused as described above. The solid thus obtained was washed with water and recrystallized to give IIb or IIc.

The charcterization data of the compounds, thus prepared, are as follows:

2-[5-(4-Benzylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilide (IIa_1): m.p. 110° (ethanol-water), yield 65% (Found: N, 16.0. $C_{21}H_{17}N_5O_2S_2$ requires N, 16.1%); IR: 1670 (C=O in a five-membered ring), 1540 (C=N), 1690 (C=O amidic) 3400 (NH).

2-[5-(4-Salicylidene-2-methyl-5-oxo-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilide (IIa_2): m.p. 135° (ethanol-water), yield 60% (Found: N, 15.5. $C_{21}H_{17}N_5O_3S_2$ requires N, 15.5%). 2-[5-(2-Methyl-5-oxo-4-vanillylidene-2-imidazolin-1-yl)-1,3,4-thiadiazol-2-ylthio]acetanilide (IIa_3): m.p. 130° (ethanol-water), yield 60% (Found: N, 14.6. $C_{22}H_{19}N_5O_4S_2$ requires N, 14.6%). *o*-(4-Benzylidene-2-methyl-5-

Table 1 – Characterization data of mannich bases (III) and styryl derivatives (IV)

Compd	R	R′	Ar	m.p.	Yield (%)	Mol. formula	N (%)	
							Found	Calc.
IIIa	H	A	4-Cl·C_6H_4	105	70	$C_{28}H_{23}N_6O_2S_2Cl$	14.5	14.6
IIIb	H	A	2-$OCH_3C_6H_4$	110	70	$C_{29}H_{26}N_6O_3S_2$	14.5	14.7
IIIc	H	A	3-Cl·C_6H_4	107	60	$C_{28}H_{23}N_6O_2S_2Cl$	14.6	14.6
IIId	H	A	2-Cl·4-NO_2·C_6H_3	210	70	$C_{28}H_{22}N_7O_4S_2Cl$	15.5	15.8
IIIe	H	A	2-CH_3·C_6H_4	175	70	$C_{29}H_{26}N_6O_2S$	15.1	15.2
IIIf	H	A	3-CH_3·C_6H_4	202	68	$C_{29}H_{26}N_6O_2S_2$	15.2	15.2
IIIg	3-OCH_3·4-OH	A	4-Cl·C_6H_4	129	72	$C_{29}H_{25}N_6O_4S_2Cl$	13.6	13.5
IIIh	H	B	4-Cl·C_6H_4	119	70	$C_{25}H_{20}N_3O_3Cl$	9.3	9.4
IIIi	H	B	3-Cl·C_6H_4	133	65	$C_{25}H_{20}N_3O_3Cl$	9.2	9.4
IIIj	H	B	2-Cl·C_6H_4	136	68	$C_{25}H_{20}N_3O_3Cl$	9.2	9.4
IIIk	H	C	4-Cl·C_6H_4	140	65	$C_{24}H_{18}N_4O_2Cl$	13.0	13.0
IVa	2-OH	A	2-OH·C_6H_4	120	60	$C_{28}H_{21}N_5O_4S_2$	12.5	12.6
IVb	H	B	2-OCH_3·4-OH·C_6H_3	124	68	$C_{26}H_{20}N_2O_5$	6.3	6.3
IVc	H	B	4-$N(CH_3)_2$·C_6H_4	63	72	$C_{27}H_{23}N_3O_3$	9.4	9.6
IVd	H	B	2-OH·C_6H_4	95	70	$C_{25}H_{18}N_2O_4$	6.6	6.8
IVe	3-OCH_3·4-OH	B	4-$N(CH_3)_2$·C_6H_4	65	65	$C_{28}H_{25}N_3O_5$	8.7	8.7
IVf	3-OCH_3·4-OH	B	3-OCH_3·4-OH·C_6H_3	175	63	$C_{27}H_{23}N_2O_7$	5.5	5.7
IVg	3-OCH_3·4-OH	B	2-OH·C_6H_4	119	64	$C_{27}H_{20}N_2O_6$	6.0	6.1
IVh	3-OCH_3·4-OH	B	3,4-$(OCH_3)_2$·C_6H_3	174	68	$C_{28}H_{23}N_2O_7$	5.6	5.6
IVi	H	C	2-OH·C_6H_4	102	65	$C_{24}H_{17}N_3O_3$	10.6	10.6

For A, B and C see Scheme I

oxo-2-imidazolin-1-yl)benzoic acid (IIb_1): m.p. 175° (methanol-water), yield 65% (Found: N, 9.1. $C_{18}H_{14}N_2O_3$ requires N, 9.2%); MS: m/z 306 (M^+),291, 163, 105 (base peak) and 77.

o-(2-Methyl-5-oxo-4-vanillylidene-2-imidazolin-1-yl)benzoic acid (IIb_2): m.p. 180° (methanol-water), yield 66% (Found: N, ~ 9. $C_{19}H_{16}N_2O_5$ requires N, 8.0%).

4-Benzylidene-2-methyl-1-nicotinoyl-2-imidazolin-5-one (IIc): m.p. 145° (methanol-water), yield 60% (Found: N, 14.4. $C_{17}H_{13}N_3O_2$ requires N, 14.4%); MS: m/z 291 (M^+), 143, 148, 128, 77, 43 (base peak).

2-{5-[2-(2-Arylaminoethyl)-4-arylidene-5-oxo-2-imidazolin-1-yl]1,3,4-thiadiazol-2-ylthio}acetanilides, o-[2-(2-arylaminoethyl)-4-arylidene-5-oxo-2-imidazolin-1-yl]benzoic acids and 2-(2-arylaminoethyl)-4-arylidene-1-nicotinoyl-2-imidazolin-5-ones (III)

A mixture of II (0.01 mole), arylamine (0.01 mole) and formaldehyde (0.015 mole) in ethanol was stirred at room temperature for 1 hr and then refluxed for 6 hr, concentrated, cooled and suspended in ice cold water. The solid thus separated was filtered washed with water and recrystallized to give III (Table 1).

2-{5-[4-Arylidene-2-(substituted styryl)-5-oxo-2-imidazolin-1-yl]1,3,4-thiadiazol-2-ylthio}acetanilides, o-[4-arylidene-2-(substituted styryl)-5-oxo-2-imidazolin-1-yl]benzoic acids and 4-arylidene-2-(substituted styryl)-1-nicotinoyl-2-imidazolin-5-ones (IV)

A mixture of II (0.01 mole), aryl aldehyde (0.01 mole) and piperidine (0.01 mole) in ethanol was refluxed for 8 hr on a water-bath, concentrated, cooled and suspended in ice cold water. The solid separated was filtered, washed with pet. ether and recrystallized to give IV (Table 1).

The mass spectrum of 4-benzylidene-2-(2-hydroxystyryl)-1-nicotinoyl-2-imidazolin-5-one (IVi) exhibited significant peaks at m/z 395 (M^+) 119, 276 and 105 (base peak).

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Antiinflammatory agents: Part X†—Synthesis and antiinflammatory activity of some new 4-[5-formyl(acyl)-2-furanoxy]-phenylalkanoic acid esters‡

C R Sarma*, R R Krishna & D R Shridhar
Chemistry Division
and
C Seshagiri Rao & (Mrs) V Taneja
Pharmacology Division, IDPL Research Centre,
Hyderabad 500 037

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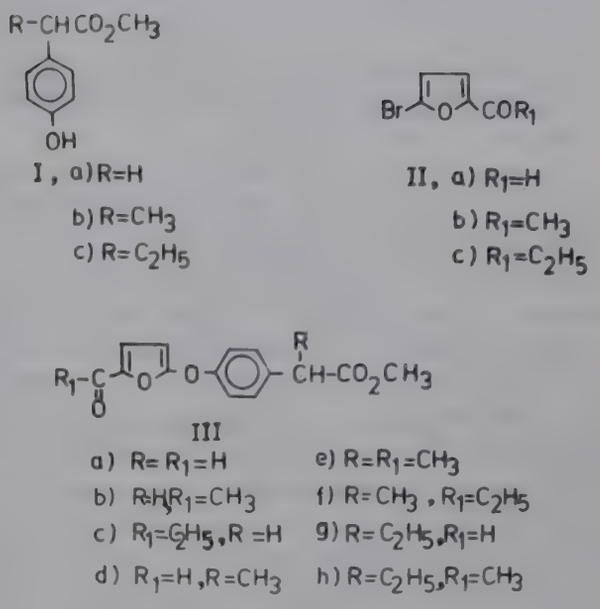
Some 4-[5-formyl(acyl)-2-furanoxy]phenylakanoic acid esters (III) have been synthesised and evaluated for their antiinflammatory activity. Methyl 4-[5-formyl-2-furanoxy]phenylacetate (IIIa) shows promising activity comparable to phenylbutazone.



Some arylalkanoic acids like neproxen, ibuprofen are widely used non-steroidal antiinflammatory drugs (NSAID). However, their prolonged use is attended by damage to gastrointestinal tract. We have synthesised several phenylalkanoic acid derivatives[1], of which methyl 4-(3-thienyl)phenyl-α-methyl acetate (IDPH 8261) appears very promising[2]. Structural modifications involving replacement of thienyl moiety with substituted furanoxy function has led to a new series of furanoxyphenylalkanoic acid esters (III), some of which possess promising antiinflammatory activity[3]. The present note describes the chemistry and antiinflammatory activity of the title furanoxyphenylalkanoic acids.

Chemistry

The starting *p*-hydroxyphenylalkanoic acids were prepared by diazotisation followed by hydrolysis of the corresponding *p*-amino acids[4]. Esterification (MeOH/conc. H_2SO_4) of the *p*-hydroxyphenylalkanoic acids afforded the required methyl esters (Ia-c). Treatment of 5-bromo-2-furaldehyde (IIa)[5] with diazomethane following the method of Gilman *et al.*[6] yielded methyl 5-bromo-2-furyl ketone (IIb).

Ethyl 5-bromo-2-furyl ketone (IIc) was prepared similarly. Condensation of IIa with methyl *p*-hydroxyphenyl acetate (Ia) in DMSO under the conditions discussed earlier[7] led to the desired compound IIIa in extremely poor yield (~5%). However, condensation of Ia-c with IIa-c in the presence of sodium in boiling toluene instead of DMSO furnished IIIa-h in better yields. The physical data of various compounds prepared are listed in Table 1.

The structures III reported in Table 1 were based on their correct elemental analyses and further supported by IR and PMR spectra (see Experimental).

Table 1—Physical data and primary antiinflammatory screening results of the compounds (IIIa-h)

Compd	Yield (%)	m.p.[a] (°C)	Mol. formula[b]	Anti-inflammatory activity[c] (% inhibition)
IIIa	23	61-62	$C_{14}H_{12}O_5$	47.09
IIIb	21	53-54	$C_{15}H_{14}O_5$	34.14
IIIc	10	36-37	$C_{16}H_{16}O_5$	8.16
IIId	30	34	$C_{15}H_{14}O_5$	8.85
IIIe	20	38-39	$C_{16}H_{16}O_5$	16.3
IIIf	10	44-45	$C_{17}H_{18}O_5$	27.84
IIIg	18	28-29	$C_{16}H_{16}O_5$	Nil
IIIh	19	45-46	$C_{17}H_{18}O_5$	6.47

(a) Recrystallised from pet. ether (40-60°C).
(b) All the compounds gave satisfactory C and H analyses.
(c) All the compounds were tested by oral route. Numbers describe the per cent inhibition of carrageenin-induced oedema in rats. The LD_{50} in mice, i.p. is 1000 mg/kg for all the compounds.

†For Part IX, see *Indian J Chem*, 25B (1986) 989
‡Communication No. 148 from IDPL Research Centre, Hyderabad 500 037.

Antiinflammatory activity

ALD_{50} studies and gross behavioural effects of all the compounds reported in Table 1 were carried out in mice following standard procedures while the antiinflammatory activity was evaluated by carrageenin-induced oedema test in rats at 200 mg/kg dose according to the procedure of Winter *et al.*[8] and the results are included in Table 1.

Compounds IIIa-h were well tolerated by mice as evidenced by their ALD_{50} values (1000 mg/kg, i.p.). The antiinflammatory screening results (Table 1) indicate that all compounds, except IIIg showed moderate to fair activity, IIIa being the most active (47.09% inhibition). The antiinflammatory activity of IIIa was studied in greater detail in comparison with standard drugs like phenylbutazone and indomethacin. The results indicate that IIIa is almost equipotent to phenylbutazone in carrageenin-induced oedema test, but less active than indomethacin. In the Cotton-Pellet test[9], the activity of IIIa at 100 mg/kg dose was found to be equivalent to that of indomethacin at 3 mg/kg, the maximum tolerable dose. The antiinflammatory activity elicited by IIIa was unaltered when tested in adrenalactomised rats, indicating that its activity is independent of adrenal pituitory axis. However, IIIa was found to be inactive when tested for its activity against adjuvent-induced polyarthritis in rats. In addition to the above, IIIa also showed moderate analgesic activity by exhibiting 55.43% antagonism against phenylquinone-induced writhing in mice at 200 mg/kg, i.p. dose, but was inactive in Ramdall-Selitto test. IIIa possesses a low order of antipyretic activity by showing a fall of 1°C at 1/5th of ALD_{50} dose.

Experimental

Melting points were determined in closed capillaries using a sulphuric acid bath and are uncorrected. IR specra were recorded in nujol on a Perkin-Elmer 237 grating spectrophotometer and PMR spectra on a Varian A-90 (EM 390) spectrometer using TMS as internal reference. Elemental analyses were performed using Hosley micro combustion apparatus MK 101. The purity of all the compound was routinely checked by TLC using silica gel coated plates.

Ethyl 5-bromo-2-furyl ketone (IIc)

To an ethereal solution of 5-bromo-2-furaldehyde (10.5 g, 0.06 mole) was added an ethereal solution of diazoethane, obtained from 70 g of nitrosoethyl urea, in two equal portions at room temperature during 4 days. Removal of ether resulted in a red solid which was treated with 10% aq. sodium bisulphite (200 ml) with stirring on a steam-bath for 2 hr. The reaction mixture was cooled, filtered and the resulting red solid was thoroughly washed with water and dried. Recrystallisation from pet. ether furnished IIc, as pale yellow shining plates m.p. 60-61°; yield 7.05 g (56%); IR (nujol); 3150, 3100 (C−H furan) and 1660 cm^{-1} (−C=O); PMR (CCl_4): δ 7.0 (d, 1H, C_3-H, J = 4 Hz), 6.5 (d, 1H, C_4-H, J = 4 Hz), 2.6 (Q, 2H, $-CH_2$), 1.05 (t, 3H, $-CH_3$) (Found: C, 41.2; H, 3.4. $C_7H_7BrO_2$ requires C, 41.4; H, 3.4%).

Methyl 4-[5-formyl-2-furanoxy]phenylacetate (IIIa)

To a hot solution of methyl *p*-hydroxyphenylacetae (3.3 g, 0.02 mole) in dry toluene, sodium metal (0.5 g, 0.02 mole) in small portions was added, followed by dropwise addition with stirring of a solution of 5-bromo-2-furaldehyde (3.9 g, 0.022 mole) in dry toluene (30 ml) and the reaction mixture was refluxed for 5 hr. It was filtered and the solvent was removed completely *in vacuo*. The resulting viscous oil was taken in ether (50 ml) and the ether solution washed with 3% cold aq. NaOH, followed by water. Removal of ether gave a red oil which was steam-distilled to remove the unreacted bromofuraldehyde. The residue from the above steam distillation was re-extracted with ether(3 × 25 ml) and the ether extract was dried (Na_2SO_4). Removal of ether furnished a dark red oil, which was thoroughly extracted with boiling hexane. The hexane extract on cooling afforded IIIa as pale yellow needles, m.p. 61-62°; yield 1.2 g (23%); IR (nujol); 3160, 3120 (C−H, furan), 1730 ($-CO-OCH_3$) and 1650 cm^{-1} (−CHO); PMR (CCl_4); δ 9.3 (s, 1H, −CHO), 7.05-7.45 (m, 5H, phenyl and Fur. C_4-H), 5.5 (d, 1H, Fur. C_3-H, $J_{3,4}$ = 4 Hz), 3.65 (s, 3H, $-OCH_3$) and 3.6 (s, 2H, $-CH_2$) (Found: C, 64.3; H, 5.0. $C_{14}H_{12}O_3$ requires C, 64.6; H, 4.6%).

All compounds listed in Table 1 were prepared in similar manner.

Acknowledgement

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Synthesis and antifungal activity of some alkyl-substituted 4-(substituted phenoxymethyl)-2*H*-1-benzopyran-2-ones

Rajvir Singh, Raj Pal Singh & Om Parkash Malik*
Department of Chemistry & Biochemistry, Haryana Agricultural University, Hisar 125 004

and

Jagdish Kumar Makarandi
Department of Chemistry, MD University, Rohtak 124 001

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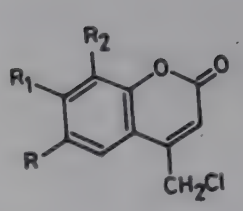
4-(Substituted phenoxymethyl)-6-*t*-butyl-2*H*-1-benzopyran-2-ones (**1-6**) and 4-(substituted phenoxymethyl)-7,8-dimethyl-2*H*-1-benzopyran-2-ones (**7-12**) have been synthesized by the condensation of appropriate 4-chloromethyl-2*H*-1-benzopyran-2-ones with various substituted phenols in the presence of potassium carbonate and dry acetone. When tested for their toxicity towards mycelial growth of seven plant pathogenic fungi in culture, *Drechslera oryzae*, *Rhizoctonia solani* and *Macrophomina phaseolina* are found to be more susceptible than *Colletotrichum falcatum*, *Fusarium solani*, *Alternaria alternata* and *Pythium aphanidermatum*. 4-(4-Nitrophenoxymethyl)-7,8-dimethyl-2*H*-1-benzopyran-2-one is the most active compound against all the fungi tested except *A. alternata* and *D. oryzae*.

In view of our recently synthesised 6-alkyl-2*H*-1-benzopyran-2-ones as potential antifungal agents[1-4], it was thought of interest to synthesise 4-(substituted phenoxymethyl)-6-*t*-butyl/7,8-dimethyl-2*H*-1-benzopyran-2-ones and evaluate their activity *in vitro* against the mycelial growth of seven plant pathogenic fungi. The results are reported in this note.



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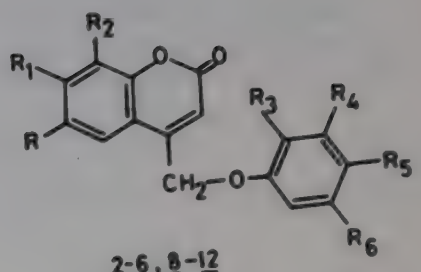

2-6, 8-12

Condensation of *t*-butylphenol and 2,3-dimethylphenol with ethyl 4-chloroacetoacetate in the presence of 73% sulphuric acid gave 4-chloromethyl-6-*t*-butyl-2*H*-1-benzopyran-2-one (**1**) and 4-chloromethyl-7,8-dimethyl-2*H*-1-benzopyran-2-one (**7**), respectively, which on treatment with various phenols such as *p*-chlorophenol,3,4-dichlorophenol,2,4,5-trichlorophenol, 4-chloro-3,5-dimethylphenol/3,4-dimethylphenol and 4-nitrophenol afforded the corresponding 4-(substituted phenoxymethyl)-6-*t*-butyl-2*H*-1-benzopyran-2-ones (**2-6**) and 4-(substituted phenoxymethyl)-7,8-dimethyl-2*H*-1-benzopyran-2-ones (**8-12**) (Table 1), respectively.

Table 1 — Physical and analytical data of 4-(substituted phenoxymethyl)-6-*t*-butyl/7,8-dimethyl-2*H*-1-benzopyran-2-ones (**1-12**)

Compd*	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	m.p. °C	PMR ($CDCl_3$ + TFA) (δ)		
									C_3H (s)	C_2CH_2O (s)	Ar-*H*(m)
1	H	H	—	—	—	—	82	120-22	6.47	—	7.20-7.70
2	H	H	H	H	Cl	H	75	128-30	6.80	5.25	7.0-7.76
3	H	H	H	Cl	Cl	H	78	172	6.50	5.15	7.0-7.75
4	H	H	Cl	H	Cl	Cl	70	228-30	6.75	5.22	6.80-7.31
5	H	H	H	CH_3	Cl	CH_3	76	215	6.65	5.52	7.0-7.50
6	H	H	H	H	NO_2	H	78	180-81	6.66	5.42	7.30-7.75
7	CH_3	CH_3	—	—	—	—	90	165-67	6.45	—	7.23-7.48
8	CH_3	CH_3	H	H	Cl	H	78	193-94	6.80	5.45	7.0-7.45
9	CH_3	CH_3	H	Cl	Cl	H	76	243	6.85	5.30	7.0-7.45
10	CH_3	CH_3	Cl	H	Cl	Cl	80	278	6.80	5.20	7.0-7.45
11	CH_3	CH_3	H	CH_3	CH_3	H	81	159	6.85	5.38	7.00-7.56
12	CH_3	CH_3	H	H	NO_2	H	79	285-86	6.66	5.42	7.15-7.82

*R = *t*-Butyl in **1-6** and H in **7-12**.

In the PMR spectrum of **1** the diagnostic C_3-H and C_4-CH_2Cl protons appeared as singlets at δ 6.47 and 4.67 respectively, while the *t*-butyl protons at position-6 appeared as a singlet at 1.37. The two *ortho*-coupled doublets centred at δ 7.48 and 7.23 with J = 8.0 Hz were assigned to the aromatic protons in **7**. Similarly in the PMR spectra of the compounds **6** and **12**, the two aromatic protons *ortho* to nitro group in phenoxy moiety appeared most downfield as a doublet around δ 8.3 with J = 10 Hz while the two protons *ortho* to O-CH_2 group appeared upfield around 7.15 also as a doublet (J = 10 Hz). The remaining protons appeared at their usual positions as given in Table 1. Thus, the PMR spectra of all the compounds were in accordance with the proposed structures and the 2-pyrone structure of all the compounds followed from the mode of synthesis and was further supported by the appearance of bands around 1710 cm^{-1} in their IR spectra[5].

Fungitoxicity

It was determined by the methods described earlier[1]. The data given in Table 2 reveal that 2*H*-1-benzopyran-2-one derivatives exhibit different degrees of activity against different fungi. Structure activity relationship studies showed that incorporation of chloro/nitro substituent in the phenoxymethyl moiety at position-4 enhances the toxicity significantly. The nitro compounds **6** and **12** exhibited a strong nonspecific fungitoxicity and the chloro derivatives **9** and **10** specific fungitoxicity towards *R. solani*. These compounds deserve further investigation for their possible use in controlling the plant diseases.

Experimental

Melting points were determined in a sulphuric acid-bath and are uncorrected. Homogeneity of the compounds was routinely checked by TLC on silica gel G using benzene or methanol-benzene as the mobile phase. IR spectra were recorded in KBr on a Perkin-Elmer 137 infracord and PMR specra in $CDCl_3$ on a Varian A60 D or R-32 (90 MHz) spectrometer using TMS as internal reference. Only those spectral data have been mentioned which have a direct bearing on the assignment of the structures. C and H analyses of all the compounds were within ± 0.5% of the calculated values.

4-Chloromethyl-6-t-butyl or 7,8-dimethyl-2*H*-1-benzopyran-2-one (**1** or **7**): General procedure

A mixture of ethyl 4-chloroacetoacetate (0.01 mole) and *t*-butyl or 2,3-dimethylphenol (0.01 mole) was stirred in an ice-bath during the addition of six volumes of 73% sulphuric acid. The mixture was kept at room temperature for 24-36 hr when the reaction was found to be complete as monitored by TLC. It was then poured over crushed ice, and the solid product collected, washed with water, dried and crystallised from benzene-pet. ether or methanol to give **1** or **7**.

4-(Substituted phenoxymethyl-6-*t*-butyl or 7,8-dimethyl-2*H*-1-benzopyran-2-one (**2-6** or **8-12**): Geneal procedure

A mixture of 4-chloromethyl-6-*t*-butyl or 7,8-dimethyl-2*H*-1-benzopyran-2-one (**1** or **6**; 0.01 mole), substituted phenol (0.01 mole), dry acetone (30 ml) and anhyd. potassium carbonate was refluxed for 16 hr and completion of the reaction monitored by TLC. The mixture was evaporated under reduced pressure and the residue triturated

Table 2—Fungitoxicity (EC_{50} values in μg ml^{-1}) of 4-(substituted phenoxymethyl)-6-*t*-butyl or 7,8-dimethyl-2*H*-1-benzopyran-2-ones

Compd	*P. aphani*	*C. falc.*	*A. alternata*	*D. oryzae*	*F. solani*	*M. phaseol*	*R. solani*
1	> 100	> 100	> 100	87	a	> 100	32
2	> 100	38.90	> 100	23	> 100	82	> 100
3	48	a	> 100	85	> 100	29	80
4	> 100	> 100	12	18	11.75	17	14
5	> 100	> 100	> 100	> 100	> 100	a	> 100
6	34	14	2.5	12	2	5	> 100
7	> 100	> 100	> 100	a	a	a	> 100
8	> 100	> 100	> 100	> 100	> 100	> 100	36
9	86	48	97	> 100	> 100	32	2.2
10	> 100	12	42	8	55	32	1
11	> 100	> 100	a	54	> 100	44	41
12	1	14	> 100	46	1	13	1

a = no growth inhibition even at 100 μg ml^{-1}.

with cold water. The solid product thus obtained was filtered, dried and crystallised from benzene or xylene-pet. ether to give 4-(substituted phenoxymethyl)-6-*t*-tutyl or 7,8-dimethyl)-2*H*-1-benzopyran-2-one in a good yield.

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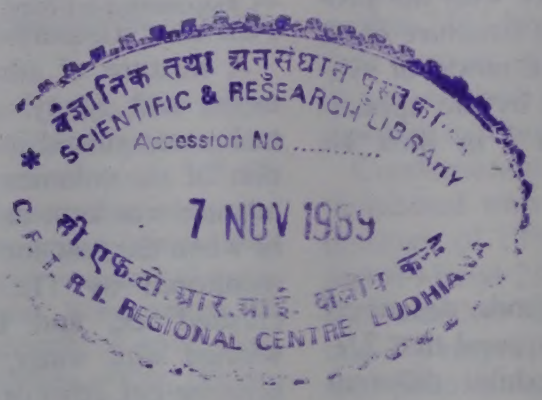

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